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CONTENTS OF PREVIOUS NUMBERS

MARCH, 1925. NUMBER 2

Abnormal Arteriovenous Communications, Acquired and Congenital. I. Report of a Series of Cases. Mont R. Reid, M.D., Cincinnati.

Splenic Anemia. A Study of End-Results With and Without Splenectomy, Based on Thirty-Five Cases. Edward M. Hanrahan, Jr., Baltimore.

Splanchnic Anesthesia: An Analysis of Forty-Two Cases. William R. Meeker, M.D., Rochester, Minn.

Meckel's Diverticulum. A Report of Twelve Cases, Including One Tumor. Frank S. Mathews, M.D., New York.

The Treatment of Fractures of the Shaft of the Femur in Children. A Report of Thirty-Two Cases. Lloyd B. Johnson, M.D., Cincinnati.

Lymphaticostomy. An Experimental and Clinical Study of Thoracic Duct Drainage in General Peritonitis. Edwin P. Lehman, M.D., and Glover H. Copher, M.D., St. Louis.

Tuberculosis of Joints. A Study of a Complete Specimen. Leonard W. Ely, M.D., San Francisco.

Liver Function in Acute Intestinal Obstruction. Ralph Colp, M.D., New York, and Henry W. Louria, M.D., Brooklyn.

Injuries to Carpal Bones: Fracture of the Scaphoid and Dislocation of the Semilunar. F. F. McGauley, M. D., Schenectady, N.Y.

A Review of Urologic Surgery. A. J. Scholl, M.D., Los Angeles; E. Starr Judd, M.D., Rochester, Minn.; Linwood D. Keyser, M.D., Roanoke, Va.; Gordon S. Foulds, M.D., Toronto, and Jean Verbrugge, Antwerp, Belgium.

MAY, 1925. NUMBER 3

The Treatment of Infections and Infectious Diseases with Mercurochrome-220 Soluble. An Analysis of Two Hundred and Ten Cases That Furnish Many Definite Examples of a Therapia Sterilisans Magna. Hugh H. Young, M.D.; J. H. Hill, M.S., and W. W. Scott, M.D., Baltimore.

Exhaustion. VIII. Anaphylaxis; Pregnancy. G. W. Crile, M.D., Cleveland.

Hypernephroma and Carcinoma of the Kidney; A Comparative Study. D. K. Rose, M.D., St. Louis.

Separation of the Upper Epiphysis of the Radius. Albert H. Montgomery, M.D., Chicago.

Embolectomy. Report of a Case. Arthur M. Dickson, M.D., Albany, N.Y.

Treatment of Epiphyseal Separation of the Lower End of the Radius. Isadore Zadek, M.D., New York.

The Effect of the Unit Record System and Improved Organization on Hospital Economy and Efficiency. M. W. Openchowski, M.D., New York.

The Deposition of Calcium Phosphate and Calcium Carbonate in Bone and in Areas of Calcification. James Crawford Watt, M.D., Toronto.

Abnormal Arteriovenous Communications. Acquired and Congenital. II. The Origin and Nature of Arteriovenous Aneurysms. Cirsoid Aneurysms and Simple Angiomas. Mont R. Reid, M.D., Cincinnati.

Twenty-Sixth Report of Progress in Orthopedic Surgery. Nathaniel Allison, M. D.; Philip D. Wilson, M.D.; Robert Soutter, M.D.; Harry C. Low, M.D.; Murray S. Danforth, M.D.; C. Herman Bucholz, M.D.; Lloyd T. Brown, M.D.; M. N. Smith-Petersen, M.D., and Robert B. Osgood, M.D.

JULY, 1925. NUMBER 1

Basal Metabolic Rates and Their Relation to End-Results in Thyroid Disease. A Statistical Study. Sara M. Jordan, M.D., Boston.

Appendectomy. A Study in Technic. C. A. Roeder, M.D., Omaha.

Abnormal Arteriovenous Communications, Acquired and Congenital. III. The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures. Mont R. Reid, M.D., Cincinnati.

Epithelioma of Cavities and Internal Organs of the Head and Neck. Albert C. Broders, M.D., Rochester, Minn.

Enchondroma of the Femur. Report of a Case with Repeated Recurrences and Ultimate Death. Robert G. LeConte, M.D.; Walter Estell Lee, M.D., and William P. Belk, M.D., Philadelphia.

The Relationship Between the Pathologic and Clinical Aspects of the Diseases of the Thyroid Gland. Henry C. Falk, M.D., New York.

Experimental End-to-End Anastomoses of the Colon. An Anatomic Study. Ferdinand C. Lee, M.D., Baltimore.

Injury, Including Irritation and Cancer. William M. L. Coplin, M.D., Philadelphia.

Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs. Walter Hughson, M.D., Baltimore.

A Review of Urology Surgery. Transplanted Muscle in Resection of the Kidney. Albert J. Scholl, M.D., Los Angeles; E. Starr Judd, M.D., Rochester, Minn.; Linwood D. Keyser, M.D., Roanoke, Va.; Gordon S. Foulds, M.D., Toronto, and Jean Verbrugge, M.D., Antwerp, Belgium.

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ARCHIVES OF SURGERY

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VARIATIONS IN BLOOD SUGAR IN RELATION TO OPERATION ON THE THYROID GLAND*

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INTRODUCTION

Blood Sugar.—Variations in the amount of sugar in the blood occur from many different physiologic and pathologic causes. In recent years, determination of the blood sugar in clinical cases has become of great importance, especially in diabetes. It has also been used experimentally in many fields of research. No attempt will be made to review again the literature of this subject, as this was done by McLeod,[1] in 1921. Since then, all the insulin[2] work has increased many fold the already enormous literature.

The important thing for us to remember is that, although the normal fasting and resting blood sugar is quite constant, many different factors can raise or lower it. The chief physiologic factors involved in its control and the difficulties in studying them have been well summarized by McLeod.[1]

Addition of glucose to the blood may be the result of: (*a*) absorption from the intestine; (*b*) hydrolysis of glycogen, particularly in the liver (glycogenolysis); (*c*) new formation of glucose out of noncarbohydrate substances, such as amino-acids (gluconegenesis). Disappearance of glucose may be the result of: (*a*) oxidation in the tissues; (*b*) excretion, mainly by the kidneys; (*c*) polymerization into glycogen; (*d*) conversion into noncarbohydrate substances, such as fat. The blood sugar is determined in order to throw light on the behavior of one or other of these processes, but the results can only be of value provided that the processes other than the one under investigation are maintained at a constant level of activity. Failure to recognize this principle has been responsible for a considerable amount of confusion in the interpretation of the causes for variations in the concentration of the blood sugar.

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* From the Third Surgical Service of the Massachusetts General Hospital.

1. McLeod, J. J. R.: Physiological Rev. **1**:208 (April) 1921.
2. Banting, F. G., et al.: Am. J. Physiol. **62**:162 (Sept.) 1922.

Hyperglycemia occurs in diabetes, after meals, exercise,[3] hemorrhage,[4] asphyxia [5] and piqûre,[6] as well as following the use of many drugs, of which epinephrin,[7] ether,[8] chloroform [9] and phenol [10] are the most important. Hypoglycemia is found most strikingly after overdosage with insulin and in acute exhaustion,[11] but also although to a less degree, in tetany,[12] guanidin poisoning,[12] after taking sodium carbonate,[13] and, in a few cases, apparently spontaneously.[14]

The effects of surgical operations on the blood sugar have been studied by Dewes [15] and by Epstein and Aschner.[16] These workers found that the general tendency of surgical anesthesia and operations is to cause an increase in the amount of sugar in the blood, if the procedure is serious or prolonged enough to cause any change at all. In seventeen laparotomies and seven peripheral operations under procain anesthesia Dewes found a rise, often to a considerable extent, in twenty of the cases. He used morphin, from 0.01 to 0.015 gm., as preliminary medication, and procain, from 0.15 to 1 gm., and epinephrin, from 0.00015 to 0.0005 gm., locally in each case. Both the epinephrin and the morphin have been shown to raise the level of the blood sugar. Also his figures of preoperative sugars varied from 40 to 180 mg. per hundred cubic centimeters. These limits are so much beyond the levels that we now consider normal that his results can only be considered very rough approximations. Epstein and Aschner studied four minor operations done under local anesthesia without finding any change in the sugar level. Five cases in which gas-oxygen anesthesia was used showed an

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3. Brösamlen, O., and Sterkel, H.: Deutsch. Arch. f. klin. Med. **130**:358 (Oct.) 1919.

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14. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

15. Dewes, H.: Arch. f. klin. Chir. **122**:173, 1922.

16. Epstein, A. A., and Aschner, P. W.: J. Biol. Chem. **25**:151 (May) 1916.

increase in the blood sugar of from 10 to 30 mg. per hundred cubic centimeters. Sixty cases under ether were found to have a very marked rise in many cases (over 100 mg. per hundred cubic centimeters) and some rise in all but three. All the determinations were made soon after operation. We will show later that the highest point in the postoperative blood sugar is reached at the end of the operation, or within the first two hours after it, and that a gradual fall lasting from four to twenty-four hours follows.

Blood Sugar in Hyperthyroidism.—The fasting blood sugar in patients with disease of the thyroid gland is within normal limits,[17] but there is a definite hyperglycemia after ingestion of glucose or administration of suprarenin.[18] In the normal person, ingestion of 100 gm. of glucose is followed by an appreciable rise in blood sugar, seldom above 160 mg. per hundred cubic centimeters. In the hyperthyroid patient, the rise may be high, even above 200 mg., but not as high as in moderately severe diabetes. The duration of this hyperglycemia is usually shorter than in diabetes. A great deal of work has been done on this "glucose tolerance" test in hyperthyroidism, but no correlation has been proved between the height of the basal metabolism and the degree of abnormality of the tolerance curve. However, practically all patients with a definite elevation in basal metabolism (+ 20 or more) show this reaction.

Since there is an apparent contradiction between the increased total oxidation in hyperthyroidism, as shown by the elevated metabolic rate, and the inability to deal rapidly with considerable amounts of glucose, as shown by the decrease of glucose tolerance, it becomes of interest to study the glucose metabolism of these patients after operation, accompanied as it frequently is by sudden increase in metabolic rate, nervous restlessness, fear and occasional persistent vomiting. It is reasonable to suppose that there is an even greater combustion of carbohydrates under these conditions than the already large amount consumed by resting hyperthyroid patients, who so frequently lose weight on a high caloric diet, and that the stored glycogen might be used more rapidly than in normal subjects. Further, we do not know that these patients always have a normal amount of glycogen in reserve, but, as far as we know, no studies have been made on this subject.

From these considerations a reduction of the blood sugar to below the normal limits under the stress of operation would not seem impossible.

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17. Denis, W.; Aub, J. C., and Minot, A. S.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. **20**:964 (Dec.) 1917.

18. Sainton, P.; Schulmann, E., and Justin-Besauçon: Bull. et mém. Soc. méd. d. hôp. d. Par. **45**:1298 (July 29) 1921; Presse méd. **29**:735 (Sept. 14) 1921.

One of the dangers of operation in patients with exophthalmic goiter has been in a severe postoperative reaction apparently toxemic in character, associated with great restlessness and nervousness, rapid pulse, a high temperature and vomiting, ending not infrequently in coma and death. Since it has been shown that the hypoglycemia produced by insulin may cause a reaction varying in severity with the level to which the blood sugar falls,[2] and possibly fatal, if untreated by measures to restore the blood sugar, it becomes of importance to determine whether, as suggested by Holman, there is a hypoglycemic factor in the reaction following operation for goiter with hyperthyroidism.

No studies of the blood sugar after thyroid operation have been reported on any large series of cases. However, Holman,[19] in 1923, published a report on three patients. This report is of especial interest because during a very severe and alarming attack of postoperative hyperthyroidism in one of the patients the blood sugar was found to be 48 mg. per hundred cubic centimeters. This patient responded very well to the administration of glucose. His other two patients did not have a severe reaction. Both showed a rise in blood sugar, with subsequent return to slightly subnormal figures twenty-four hours later.

PURPOSE OF STUDY

Postoperative Blood Sugar.—In view of the considerations outlined, it seemed desirable to study a considerable number of the patients operated on in our thyroid clinic. We wished, first, to determine whether any of our patients were showing a hypoglycemic reaction after operation. It was also possible that the blood sugar might be used to predict a severe reaction at an earlier period than is possible by purely clinical observation. Our data show the blood sugar under ordinary postoperative care without any change being made from our previous routine in the treatment or feeding of the patients.

Preoperative Blood Sugar.—A few observations were made on patients before operation. This had two purposes: To secure a level from which changes in the postoperative sugar might be interpreted, and to see if the emotional strain immediately before operation caused any hyperglycemia.

METHODS

On admission to the hospital, our patients are put to bed and kept there. They are studied by the medical service, and rested until no further benefit from rest seems likely. Toward the end of the period in which this study was made, we began to use compound solution of iodin as a preoperative treatment in addition to rest, so that part only

19. Holman, E. F.: Bull. Johns Hopkins Hosp. **34**:69 (Feb.) 1923.

of our patients received this. A few days before operation, the patients are moved to private rooms. The routine preoperative medication is morphin, from 0.015 to 0.030 gm., and atropin, 0.0005 gm. The anesthetic is nitrous oxid and oxygen. From 20 to 50 c.c. of 1 per cent. procain is used locally. In about half the cases, a small amount of ether has to be given with the nitrous oxid, but not over 30 c.c. in any case. The anesthesia varied in length from fifteen minutes to one hour.

After operation, 0.010 gm. morphin, hypodermoclysis of 1 liter of salt solution, and proctoclysis of 500 c.c. of tap water are given on arrival from the operating room. These are all done before the patient is fully conscious. Later, the morphin is repeated as necessary, and 250 c.c. of water or 5 per cent. glucose is given by rectum every four hours until the patient drinks fluids freely. The patients are encouraged to drink water and orange juice, even before their nausea has ceased.

TABLE 1.—*Blood Sugar Before Operation**

Case	Diagnosis	Sex	Age	Basal Metabolism	Blood Sugar 24 Hours or More Before Operation	Morning of Operation: In Ward 1 Hour Before	Morning of Operation: On Operating Table 5 Minutes Before
1	E. G.	♀	35	68†	...	112	...
2	E. G.	♀	44	64	108	...	99
3	E. G.	♂	28	64	98	93	104
4	T. A.	♀	45	60†	...	129	...
5	E. G.	♀	42	58	...	112	...
6	E. G.	♀	41	56	...	99	...
7	E. G.	♂	43	55	...	143‡	107
8	E. G.	♀	44	50	93	96	...
9	T. A.	♀	56	47	...	99	...
10	E. G.	♀	44	45	93	...	...
11	E. G.	♀	54	45	85, 97	110	...
12	E. G.	♂	34	44	...	88	...
13	E. G.	♀	41	44	93	107	...
14	T. A.	♀	45	42	...	104	...
15	T. A.	♀	42	38	80	...	110
16	E. G.	♀	28	38	110, 100	...	...
17	E. G.	♀	48	38	102	99	...
18	E. G.	♀	24	37	...	84	...
19	E. G.	♀	44	36	103	93	...
20	E. G.	♀	38	35	...	...	100
21	E. G.	♀	40	32	117	...	93
22	E. G.	♀	40	28	82	...	...
23	E. G.	♀	31	26#	...	120	...
24	E. G.	♀	26	24#	...	99	...
25	E. G.	♀	24	24#	...	89	91
26	E. G.	♀	36	23#	96	111	...
27	E. G.	♀	46	22#	...	90	...
28	E. G.	♀	37	8#	...	105	...
29	E. G.	♀	39	8#	...	95	...
Average					97	102	100

* In this and the succeeding tables, B. S. means blood sugar in milligrams per hundred cubic centimeters; B. M., basal metabolism; E. G., exophthalmic goiter; T. A., adenomatous goiter with hyperthyroidism, and ♂ signifies male, ♀ female.

† In this and Table 2, basal metabolism determinations made some weeks before operation and probably not a true index of the patient's condition. In all cases, the most recent determination was used and this was, in all other cases, within two days of the operation.

‡ Operation at noon under 0.08 gm. of morphin and 16 c.c. of paraldehyd, together with 70 c.c. of 1 per cent. procain. No nitrous oxid was given. All other operations were at 9 a. m. First sugar was three hours before operation.

§ The patient had taken carbohydrate food shortly before the blood for the sugar determination was taken. These are excluded from the averages.

The patient had preoperative compound solution of iodin treatment.

The samples of blood for determination were taken at different intervals. It was very soon found that a specimen taken within thirty minutes after operation, another six hours later, and another after twenty-four hours, would show any important changes. The specimens were collected over oxalate and preserved with a drop of formaldehyd.[20] The determination was made under the direction of Dr. J. H. Stoddard by the method of Folin and Wu.

COMMENT ON TABLES

Table 1 shows that there is no appreciable difference in the blood sugar on the morning of operation in comparison with previous observations; also, that there is no marked change during the final preparation and transfer to the operating room.

The two factors affecting these patients that might cause hyperglycemia are fear and morphin. The latter probably is not active except in doses much larger than used in human therapeutics. In fear, as well, which probably causes hyperglycemia through stimulation of the secretion of epinephrin, small degrees are not sufficient to cause any change in the sugar level.

Our results are not surprising in view of the efforts now being made by our clinic as well as all other thyroid clinics to eliminate fear as a factor in these cases, by careful preoperative preparation. As a result, no thyroid patients are operated on when they exhibit any objective symptoms of fear except to a small degree.

TABLE 2.—*Blood Sugar After Subtotal Thyroidectomy*

					Blood Sugar					
Case	Diagnosis	Sex	Age	Basal Metabolism	Before	After 0 to ½ Hour	After 3 to 6 Hours	After 18 to 24 Hours	After 48 Hours	After 72 Hours
1	E. G.	♀	35	68†	112	198	204	...	...	105
2	E. G.	♀	44	64	99	143	113	102	...	...
4	T. A.	♀	45	60†	129	89	100	101	...	...
6	E. G.	♀	41	56	99	99	85	...	...	...
9	T. A.	♀	56	47	99	162	100	87	...	...
15	T. A.	♀	42	38	80	110	...	...	...	...
16	E. G.	♀	28	38	105	...	118	151§	...	...
17	E. G.	♀	48	38	99	...	...	143§	141§	...
19	E. G.	♀	44	36	93	150	162	139§	...	...
20	E. G.	♀	38	35	100	106	156§	122§	...	...
22	E. G.	♀	40	28	82	159	135	118	...	...
23	E. G.	♀	31	26#	120	160	180	175§	144§	...
24	E. G.	♀	26	24#	99	85	127	148§	101	...
26	E. G.	♀	36	23#	111	174	133	110	104	...
27	E. G.	♀	46	22#	99	178	165	149	109	...
28	E. G.	♀	37	8#	105	172	134	105	...	...
29	E. G.	♀	39	8#	95	212	168	99	96	...
Average					101.5	152	137	106	102.5	105

20. Denis, W., and Aldrich, M.: J. Biol. Chem. **44**:203 (Oct.) 1920.

TABLE 3.—*Blood Sugar After Hemithyroidectomy*

Case	Diagnosis	Sex	Age	Basal Metabolism	Blood Sugar: Before	After 0 to ½ Hour	After 3 to 6 Hours	After 6 to 12 Hours	After 18 to 24 Hours	After 30 Hours	After 48 Hours
3	E. G.	♂	28	64	104	144	117	...	86	...	...
7*	E. G.	♂	43	55	107	152	145	...	...	...	107
11	E. G.	♀	54	45	110	141	131	149	126	96	...
12	E. G.	♂	34	44	88	107	97	86	86	...	...
14	T. A.	♀	45	42	104	152	132	...	160†	...	...
18	E. G.	♀	24	37	84	110	...	...	79	...	...
7‡	E. G.	♂	43	35	136†	....	...	...	...	...	114
12	E. G.	♂	34	35	...	...	...	...	100	...	...
21	E. G.	♀	40	32	93	165	138	...	129†	...	...
25	E. G.	♀	24	24	91	128	128	...	109	...	...
Average					98	137	127	117	98	96	110

* This patient was prepared for operation by morphin sulphate, 0.03 gm., and paraldehyd, 16 c.c., in this operation and also in his second, which is marked thus ‡. Seventy cubic centimeters of 1 per cent. procain was used both times.

‡ After this operation, the patient had the most severe reaction of any we studied. However, it was not a pure hyperthyroid reaction; ten hours after operation, there was a hemorrhage which required resuture of the wound. The second day after operation, his temperature rose to 105 F., his pulse to 140, and his respiration to 50. It was found by clinical and roentgen-ray examination to be an embolic pneumonia. He recovered quite rapidly. It was during the pneumonia that the 48-hour specimen was taken.

† The patient had taken carbohydrate food shortly before the blood for the sugar determination was taken. These are excluded from the averages.

TABLE 4.—*Blood Sugar After Ligation of Thyroid Artery*

Case	Diagnosis	Sex	Age	Basal Metabolism	Blood Sugar: Before	After 0 to ½ Hour	After 3 to 6 Hours	After 6 to 12 Hours	After 18 to 24 Hours	After 30 Hours	After 48 Hours
5	E. G.	♀	42	58	112	140	...	...	...	...	...
2	E. G.	♀	44	50	96	105	99	...	...	133*	...
2	E. G.	♀	44	45	93	105	...	97	84	...	152*
6	E. G.	♀	41	44	107	122	104	...	92	...	...
Average					102	118	101.5	97	88		

* The patient had taken carbohydrate food shortly before the blood for the sugar determination was taken. These are excluded from the averages.

TABLE 5.—*Blood Sugar After More Than One Operation in Certain Cases* *

Case	Diagnosis	Operation	Basal Metabolism	Blood Sugar: Before	After 0 to ½ Hour	After 3 to 6 Hours	After 6 to 12 Hours	After 18 to 24 Hours	After 30 Hours
2	E. G.	L.1	45	93	105	...	97	84	...
		L.2	50	96	105	99	...	...	133†
		S.	64	99	143	113	...	102	...
6	E. G.	L.1	44	107	122	104	...	92	...
		S.	56	99	99	85	...	...	...
18	E. G.	H.1	24‡	91	128	128	...	109	...
		H.2	37‡	84	110	...	...	79	...

* In this table, L.1 means ligation of one superior thyroid artery; L.2, ligation of second superior thyroid artery; H.1, first hemithyroidectomy; H.2, second hemithyroidectomy, and S., subtotal thyroidectomy.

† The patient had taken carbohydrate food shortly before the blood for the sugar determination was taken. These are excluded from the averages.

‡ The patient had preoperative compound solution of Iodin treatment.

TABLE 6.—*Blood Sugar After Operations Under Gas-Oxygen on Patients Without Thyrotoxicosis*

Case	Diagnosis	Basal Metabolism	Operation	Duration, Min.	Blood Sugar				
					Before	After 0-½ Hr.	After 3-6 Hr.	After 18-24 Hr.	After 48 Hr.
30	Adenomatous thyroid.....	—	Hemithyroidectomy	35	144	238	148	102	92
31	Cystadenomatous thyroid	4	Excision of cyst.....	27	*92	115	144	...	...
32	Adenomatous thyroid.....	—	Hemithyroidectomy	33	94	...	125	151*	...
33	Chronic appendicitis.....	—	Appendectomy.....	25	...	153	128	85	...
34	Cystadenomatous thyroid	—	Excision of cyst.....	..	102	147	111	129*	...
35	Adenomatous thyroid.....	13	Subtotal.....	52	105	183	180	123	111
36	Cystic mastitis.....	—	Excision of both breasts.....	30	102	178	100	117	...
37	Adenomatous thyroid.....	1	Subtotal.....	37	102	210	137	106	92
	Average.....				106	175	134	106	98

* The patient had taken carbohydrate food shortly before the blood for the sugar determination was taken. These are excluded from the averages.

Operative procedures on patients with hyperthyroidism cause a transient hyperglycemia in most cases, but occasionally there is no rise. We have encountered no instances of a fall in the sugar level. The duration of the hyperglycemia is from six to twelve hours. Its height is extremely variable, and bears no definite relation to the degree of elevation of the basal metabolism rate. On the other hand, the length and severity of the operation, as shown by a comparison of the tables for subtotal thyroidectomy, hemithyroidectomy and ligations, do affect the blood sugar curve. The larger operations cause the greatest change in the blood sugar. An attempt was made to correlate the degree of rise with the following points: pulse rate before, during, and after operation; cyanosis during anesthesia; amount of ether used; temperature reaction; severity of postoperative symptoms; postoperative basal metabolism curve; duration of the disease; loss or gain of weight before operation, or age of the patient. As these were all negative, we decided not to cumber this paper with these data.

Table 6 represents data on miscellaneous patients who were studied as controls and who had operations performed under gas-oxygen anesthesia, but who were not thyrotoxic. They show changes in the blood sugar level very similar in degree and variation to those in the toxic patients.

Cause of Elevation.—It seems to be well established by our figures, as well as by others, that after surgical operations the blood sugar may remain within physiologic limits or it may rise to a considerable degree. The amount of the rise depends somewhat on the length and severity of the operation, and is greatest when ether is the anesthetic and least with procain. In patients with hyperthyroidism it is no different from what it is in others.

It is not the purpose of this paper to discuss the cause of the rise, which probably includes many factors. Increased secretion of epinephrin probably accounts for part of it; acidosis, or rather the attempt of the organism to combat acidosis, for another part. It passes off rapidly after the operation and is not followed, at least in our cases, by any appreciable negative phase.

The occurrence of this reaction suggests increased mobilization and also perhaps utilization of glucose, during and immediately after the operation.

Hypoglycemia.—Under the conditions obtaining after operation for exophthalmic goiter, a greater consumption of glucose might occur than after operations on other patients. These conditions are, besides the abnormal basal metabolism rate, fever, nervousness, twitching, restlessness and vomiting. All of these together would account for a very large demand from the tissues of the body for glucose. In extreme reactions, conditions might be produced in the organism like those in exhausted Marathon runners.

That such a condition is not only possible, but has occurred and has been studied from this point of view has been shown by Holman's case. We have found no instances of hypoglycemia in our cases, but we have had no cases of reaction in any way comparable to his since the beginning of this study. We believe his observation to be of great importance in showing what happens to the blood sugar of these patients when the demand of the tissues gets away from the supply available to the blood.

The preoperative and postoperative care should be directed to maintaining carbohydrate intake by mouth and by rectum, in all cases, and by hypodermoclysis, when indicated by the presence of severe postoperative symptoms.

CONCLUSIONS

1. There is a rise in blood sugar after operation on hyperthyroid patients similar in every way to that in other patients.

2. No case of hypoglycemia occurred in the series we have studied.

3. No emotional hyperglycemia occurred in our patients before operation.

4. Conditions following operation for exophthalmic goiter may cause increased demand for glucose.

5. Treatment should be directed to maintain the supply of glucose, bearing in mind the occurrence of hypoglycemia in the postoperative reaction reported by Holman.

THE INJECTION OF ABSOLUTE ALCOHOL INTO THE THYROID GLAND

EXPERIMENTAL OBSERVATION OF A SUGGESTED CLINICAL PROCEDURE *

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Among the early methods of treatment of enlargement of the thyroid gland is that of injection of tincture of iodin directly into the gland substance. This form of treatment grew out of the use of iodin painted over the gland area and its internal administration in cases of goiter. According to Prinz,[1] Sköldberg first proposed the method in 1855. The first reports available, however, are those of Luton,[2] 1867, and Bertin,[3] 1868. The intraglandular injection of the tincture was proposed and used first in those cases which did not show decrease in size of the enlarged gland with other forms of iodin treatment. The case reports show that those which were most benefited were simple and cystic goiters in young persons. Luecke,[4] 1868, introduced the treatment in Germany. His report shows also that of the cases so treated, those showing improvement were cases of simple and cystic types of goiter. However, at a later date, the same treatment was used by Alessandri[5] and Francesco[6] in exophthalmic cases. Both report cures. In France, toxic symptoms were held to contraindicate the use of iodin according to Lenormand,[7] and the same was true in England.[8] The reported results with the so-called parenchymatous and cystic gland

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* Work done in the department of anatomy, University of Michigan Medical School, under the direction of Dr. G. Carl Huber.

1. Prinz, A. L.: Ueber dem einfluss des Jodes auf die Schilddrüse in verband mit der Injections therapie des Kropfes, Inaugural Dissertation, Freiburg, 1895.

2. Luton, A.: Nouvelles observations d'injections de substances irritantes dans l'intimita des tissus malades, Arch. gén. de méd. **2**:438, 1867.

3. Bertin: Des injections irritantes dans l'intimite des tissus malades, Arch. gén. de méd., April, 1868.

4. Luecke: Berl. klin. Wchnschr. **5**:261, 535, 1868.

5. Alessandri, R.: Sulla natura e sulla cura del morbo di Basedow, Bull. Reale Accademia Medici di Roma **26**:441, 1900.

6. Francesco, C.: Le inienzioni di iodio ed ergatina nel morbo di Basedow, Gazz. d. osp. **27**:997, 1906.

7. Lenormand: Traitement du goitre par les injections de teirsture d'iode, Paris, 1901.

8. MacKenzie, M.: On the Treatment of Cystic and Fibrocystic Bronchocele, Tr. Clin. Soc. **7**:121, 1874.

enlargements are almost universally good. Whether these good results —decrease in size of the enlargement—were due to a local gland destruction with scar formation or to the added supply of iodin was a question of the time. Since the enlargements did not show decrease with oral administration of iodin it is fair to believe that the local irritant action played considerable part in producing the results obtained. The large number of injections which were used also favors the local action since each injection consisted of from 0.5 to 1 c.c. of the tincture; necessarily only a small area of destruction would be produced at each sitting.

The injection method continued to be used until the popularization of operative measures on the thyroid. The procedure was undoubtedly a harmless one. Prinz [1] quotes Schwalbe as reporting 1,000 compiled cases with one death from embolus due to injection of the iodin into a large vein. No untoward results are mentioned elsewhere.

Tincture of iodin, although by far the most popular solution used, was not the only one proposed for use in injecting enlarged thyroids. Mosetig-Moorhof [9] introduced a solution of iodoform 1 part, ether 5 parts and olive oil 9 parts. Frey,[10] Boechat,[11] Garré [12] and Marquet [13] report their clinical results from the injection of iodoform solution into the thyroid to be very good. However, Billroth [14] preferred the pure tincture of iodin preparations. Chlorid of iron was used by Ericksen and Alguié in parenchymatous goiters, according to Lenormand.[7] Parona [15] used chlorid of potassium and sodium. Naumann [16] tried iodid of calcium in glycerin 1:5:500. All claimed fair results, but none of these solutions came into general use.

Although injection therapy had been used clinically since 1867, there are no histopathologic reports of the gland after injection or

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9. Mosetig-Moorhof, Albert: Die Behandlung des weichen Kropfes mit parenchymatösen Injectionen von Iodoform, Wien. med. Presse **31**:1, 1890.

10. Frey: Beiträge zur Behandlung des Weichen Kropfes mit parenchymatösen Iodoform Injectionen, Wien. med. Presse **31**, No. 41, 1890.

11. Boechat: Le traitment du goitre par l'iodoforme, Cor. Bl. f. schweiz. Aerzte **10**:12, 1880.

12. Garré, Carl: Zur Kropfbehandlung mit parenchymatösen Iodoformenspritzungen, Cor.-Bl. f. schweiz. Aerzte **24**:361, 1894.

13. Marquet: Un cas de goitre sclereux guéri par les injections d'ether iodoforme, Limousin méd. **28**:23, 1904.

14. Billroth: Erfahrungen über die operative Behandlung des Kropfes, Wien. med. Presse **18**:1505, 1877.

15. Parona, Francesco: Glückliche Behandlung durch parenchymatöse Injektion von Wasser von Salsomaggiore, Rivist. Clin. d. Bologne **227**:1871; trans. in Deutsch. Klinik. **24**:383, 1872.

16. Naumann, H.: Ueber den Kropf und dessen Behandlung, 1891; translation from Swedish into German by Reyher, 1892.

experimental studies of gland tissue after injection until that of Prinz,[1] in 1895. He injected tincture of iodin and ether iodoform into cat thyroids, and removed these for study at intervals of from one to four weeks. A like quantity of 95 per cent. alcohol was injected in three cats. From this work, Prinz concluded that the chief local effect of the tincture of iodin was due to the alcohol. The report was made in the form of an "inaugural dissertation" presented at Freiburg, in 1895, under the title "Ueber dem Einfluss des Jodes auf die Schilddrüse in verband mit der Injections therapie des Kropfes." The report is inconclusive because of the small number of experiments and the short time of observation in the experiments. This report did not obtain general circulation.

With the popularization of the partial thyroidectomy, injection of the thyroid gland was seldom done because the very type of thyroid disease in which the iodin injections gave best results is the best operative risk. On the other hand, iodin injections were contraindicated in the toxic cases, in which a method of destroying gland tissue with minimal risk is highly desirable as a preliminary procedure. In an attempt to find a method that would allow destruction of gland tissue in very toxic cases with slight risk, Gatch, Beall and Mouser, in 1909, at the suggestion of Porter,[17] conducted animal experiments with injections of boiling water. As a result of these experiments and subsequent data from human thyroids injected by Porter [18] and others,[19] it was found that thyroid tissue can be destroyed in this way with minimum risk to the patient. There are certain inconveniences connected with the use of boiling water injections which have greatly limited its use. These may be summarized as follows: The difficulty with which the water is kept at the requisite temperature while the injection is being made, and the inconvenience with which any hot solution is handled. Lahey [20] used three pairs of gloves, two of rubber and between them a heavy cotton glove. Notwithstanding these objections, the method is being used in several of the larger clinics of this country as a preliminary measure to subtotal thyroidectomy, in extremely toxic patients.

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17. Porter, M. F.: The Thyroid with Special Reference to Hyperthyroidism and a New Method of Treatment, J. A. M. A. **57**:1120 (Sept. 30) 1911.

18. Porter, M. F.: Injection of Boiling Water in the Treatment of Hyperthyroidism, J. A. M. A. **61**:88 (July 12) 1913; Boiling Water Injections into the Thyroid Gland for Hyperthyroidism, Surg., Gynec. & Obst. **20**:1, 1915.

19. O'Day, J. C.: Intrathyroid Injections of Boiling Water in Hyperthyroidism, Ann. Surg. **65**:279 (March) 1917; Link, Goette: Preliminary Thyroid Operations, J. Indiana M. A. **12**:64 (March) 1919; Lahey, F. H.: Multiple Stage Measures in the Surgery of Severe Hyperthyroidism, J. A. M. A. **78**:1862 (June 17) 1922.

20. Lahey (Footnote 19, third reference).

Because of the difficulties in handling boiling water, other methods of partial gland destruction have been advanced. Watson [21] reports the use of urea and quinin sulphate. Sheehan [22] used a solution of phenol (carbolic acid), iodin and glycerin, while Mason [23] exposed the thyroid by a small incision and destroyed small portions by an electric cautery at successive sittings.

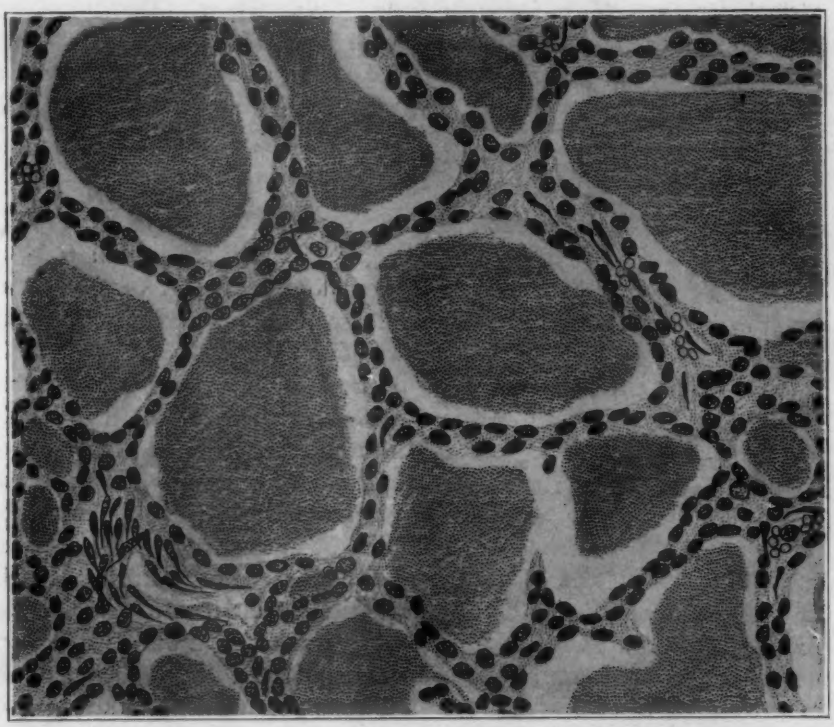

Fig. 1.—Section from normal thyroid of dog.

Because of the number of cases which fail to show marked improvement after ligation of thyroid vessels, the difficulties attending operative procedure in the very toxic cases without the use of preliminary measures, and the inherent difficulties and inconveniences connected

21. Watson, Leigh F.: Injection of Quinin and Urea Hydrochlorid in Hyperthyroidism, J. A. M. A. **62**:126 (Jan. 10) 1914; Quinin and Urea Injected in Hyperthyroidism, New York M. J. **103**:791 (April 22) 1916.

22. Sheehan, J. E.: Seventeen Cases of Goiter Treated with Injections of Carbolic Acid, Iodin and Glycerin, M. Rec. **92**:591 (Oct. 6) 1917.

23. Mason, J. T.: Mistakes in One Hundred Thyroidectomies with Description of New Method of Thyroid Cauterization in Treating Exophthalmic Goiter, J. A. M. A. **75**:160 (July 17) 1920.

with the use of boiling water as a preliminary procedure, the method perhaps most generally used, further experimentation with non-toxic solutions suitable for purposes of injection seemed not without encouragement. The success that attends the use of absolute alcohol injection [24] in the prevention of amputation neuromas led Huber to suggest the use of absolute alcohol for thyroid injection. This method seemed deserving of experimental study. The experiments undertaken and observations made form the basis of this report. Thyroid glands of eighteen dogs have been injected with from 0.5 to 10 c.c. of absolute alcohol and the injected glands removed at intervals varying from fifteen minutes to two months after the injection. Gross and microscopic observations are recorded.

METHOD

Under ether anesthesia and aseptic precautions, a 2 inch (5 cm.) midline incision was made in the thyroid region of the neck. The pretracheal muscles were separated, and the thyroid lobe brought into the wound by grasping the pericapsular tissue. Absolute alcohol was used in each case on the ground that this gave a definitely known strength, that a smaller quantity would be required to produce the same result, and that dilution by body fluids to an impotent strength would be less readily accomplished. A No. 22 bore 2½ inch ordinary Luer needle was used with a 10 c.c. Luer syringe. Injections were made deep into the gland substance, the needle being advanced from time to time during the procedure. If a relatively large amount of alcohol as compared to the size of the gland was injected, it could be seen to infiltrate the subcapsular tissue, but it did not penetrate the capsule itself. Thus, it was found that when a single puncture wound was made in the capsule there was much less loss of alcohol into the perithyroid tissues than when numerous openings were made in the capsule through which the alcohol might escape after a certain intraglandular pressure had been reached. In no case was there marked bleeding from the puncture wound owing to the rapid coagulation produced by the alcohol. After injection, the lobe was somewhat larger than before and more firm in the area of injection. When the procedure was completed, the lobe was allowed to assume its former position. The pretracheal muscles were brought together with No. 2 catgut sutures, the deep fascial edges approximated with No. 2 ten day catgut, and the skin wound was closed with silk sutures. A cotton collodion dressing was applied.

Two dogs in the series had enlarged thyroids of the colloid goiter type. In one, to palpation, each lobe was about the size of a hen's egg. The second presented a right lobe the size of a lemon, while the left

24. Huber, G. C., and Lewis, Dean: Amputation Neuromas, Their Development and Prevention, Arch. Surg. **1**:85 (July) 1920.

was somewhat larger. In these cases, the dog was given ether as usual, and the neck prepared as for operation in the previous experiments. The No. 22 bore needle was inserted through the skin and intervening tissues into the thyroid lobe, reaching this near the lower pole at the anterior mesial surface. The needle, when introduced into the gland, was free of the syringe, in order that any bleeding might be more evident, and thus the possible ill effects from injection of the alcohol directly into a vein might be prevented. The needle was directed toward the superior pole, and the approximate position of the needle point could be determined by palpating the lobe. Injection was begun with the needle well in the gland substance, and continued as the point was advanced toward the superior pole.

The largest quantity of absolute alcohol injected into an animal at one sitting was 10 c.c. In no case was there an immediate or delayed ill effect from the alcohol. Heart rate and respiration were not affected. On the second day after injection and continuing until from the fourth to the fifth day, there was moderate swelling of the injected lobe. When this began to subside on the third or fourth day, the size decreased at first very rapidly, reaching the size found previous to injection between the fifth and seventh days. Beyond this, the diminution in size continued more slowly for a period of from six to eight weeks.

PROTOCOLS

EXPERIMENT 1.—Dog 1, a medium sized dog in good health, in which the thyroid was not palpable, was operated on, fifteen minutes after the injection of alcohol, March 3, 1924, under ether anesthesia. In preparation, the neck region was shaved and cleaned with soap and water, alcohol and tincture of iodin. A 2 inch vertical midline incision was made in the thyroid region of the neck. The pretracheal muscles were separated in the midline and retracted, exposing the trachea. The left thyroid lobe was found and drawn into the wound by slight traction on the pericapsular fascia. Three cubic centimeters of absolute alcohol was injected into its lower half. The gland was removed fifteen minutes later, the right lobe being used for comparison.

The right lobe was normal in appearance. The left lobe was more firm than normal; the lower pole had a seared appearance and, on section, was edematous.

The injected area showed some broken acini with separation of the interacinous and interlobular connective tissue. The acinous cell and nuclear structure did not differ from the normal tissue.

EXPERIMENT 2.—Dog 2 was operated on, fifteen minutes after the injection of alcohol, March 3, 1924, under ether anesthesia. The dog had been prepared in the same way as Dog 1, and the procedure and the time allowed between injections and removal were the same.

The lobe had a grayish, seared appearance. The microscopic findings were the same as in Dog 1.

EXPERIMENT 3.—Dog 3 was operated on, three days after the injection of alcohol, May 8, 1924, under ether anesthesia, after preparation with soap and

water, alcohol and tincture of iodin. The right thyroid lobe was exposed as in Experiment 1, and 5 c.c. of absolute alcohol was injected deep into the lobe, after which it was replaced and the wound was closed. May 11, the wound was reopened, and the right lobe of the thyroid was removed.

The gland was swollen and very hard. The cut surface through the injected region showed a mottled gray and brown appearance.

Microscopic examination revealed that there were definite areas of coagulation necrosis with fragments of nuclei remaining. The colloid of the injected

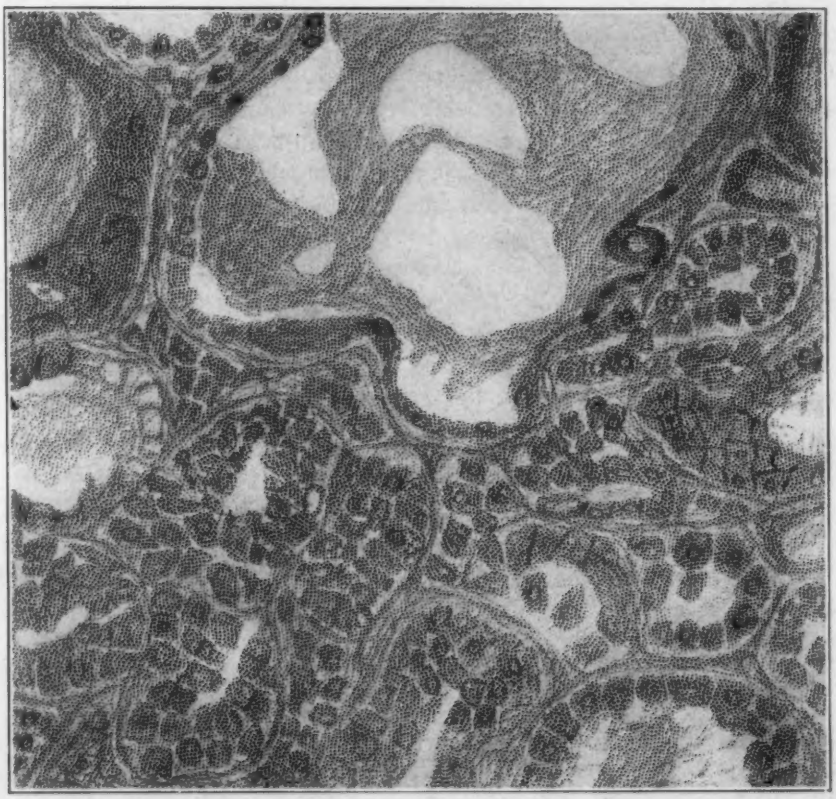

Fig. 2.—Section from dog thyroid removed fifteen minutes after injection with absolute alcohol (Dog 1).

area took the basic stain more than is normal. The blood vessels passing through the injected areas were thrombosed. There was a moderate round cell infiltration about the periphery of the areas of necrosis. Small groups of acini filled with blood were found in the injected areas and about the border of several of the areas of necrosis. The thyroid tissue about the injected regions was normal.

EXPERIMENT 4.—Dog 4 was operated on, three days after the injection of alcohol, May 8, 1924, under ether anesthesia, after preparation with soap and water, alcohol and tincture of iodin. The right thyroid lobe was exposed as

in Experiment 1 and 5 c.c. of absolute alcohol was injected deep into the lobe, after which it was replaced and the wound was closed. May 11, the wound was reopened, and the right thyroid lobe was removed. The gross and microscopic findings were similar to those in Dog 3.

EXPERIMENT 5.—Dog 5, a medium sized, apparently healthy dog, with no enlargement of the thyroid, was operated on, seven days after the injection of alcohol, Oct. 22, 1923, under ether anesthesia, after the neck region had been shaved and cleaned with soap and water, alcohol and tincture of iodin. A 2 inch (5 cm.) vertical midline incision was made in the thyroid region of the neck. The pretracheal muscles were separated in the midline and retracted, exposing the trachea. The left thyroid lobe was found, and was drawn into the wound by slight traction on the pericapsular fascia. The lobe was the size of a large almond. One-half cubic centimeter of absolute alcohol was injected deep into the gland substance. A small amount of alcohol was spilled into the wound. The wound was washed with a warm sterile saline solution, and the lobe was replaced. The thyroid had not changed in appearance following the injection. The wound was closed in layers. A cotton collodion dressing was applied. October 25, there was slight separation of the skin edges at the lower end of the wound, with a small amount of serous discharge. The wound was irrigated with surgical solution of chlorinated soda (Dakin's solution) twice daily. The dog was in good general condition. Ocotber 29, the wound was entirely healed. The dog was killed, and both lobes were removed for study. The normal right lobe was removed along with the injected left lobe for comparison.

There was no change in the size of the left lobe from that seen at the operation. The external appearance of the two lobes was similar. There was, however, a small central area of firmness in the left lobe.

Sections through the gland at the level of the area of more marked firmness showed an area of coagulation necrosis in which patches of very fainly staining acinous cell nuclei remained. There was loss of cell outline of all the acinous cells. Scattered fibroblasts were seen throughout the area of necrosis, occupying for the most part the interacinous connective tissue spaces. There were masses of newly formed fibroblasts about the area of necrosis with heavy bands of newly formed fibroblastic tissue extending toward the center of the area along the thrombosed vessels. The surrounding thyroid tissue was normal.

EXPERIMENT 6.—Dog 6, in which the thyroid was not felt, was operated on seven days after the injection of alcohol, Oct. 22, 1923, under ether anesthesia, after the same preparation as that given Dog 1. The left thyroid lobe was exposed. This proved to be the size of a large hickory nut, normal in appearance, and in consistency firm and elastic. The needle was introduced well into the gland substance near the lower pole, and 2 c.c. of absolute alcohol was injected as the needle was advanced toward the superior pole of the gland. The injected portion of the lobe became grayish and cooked in appearance. There was no general effect. The wound was closed. October 29, the wound had healed by primary union, and the dog was in good condition. The wound was reopened under aseptic precautions, and the left lobe was removed. The wound was closed.

The upper and lower poles outside the area of injection were normal in appearance. There was no change in the size of the gland from that observed before injection. In the injected region, the gland was bluish, as from old hemorrhage. On palpation, there was a definite central core which was very

hard. On section, the central core showed as an area of bluish-black with loss of structure.

On microscopic examination, the area of necrosis was revealed to be considerably larger than that of Dog 5, but of the coagulation necrosis type with evidence of blood extravasated into parts of the area. The fibrous tissue reaction was very marked. There was some round cell infiltration into the border of the area of necrosis.

EXPERIMENT 7.—Dog 7, a large brown mongrel, in which both lobes of the thyroid were palpable, was operated on eight days after the injection of alcohol, Oct. 24, 1923, under ether anesthesia, after the same preparation as that given Dog 5.

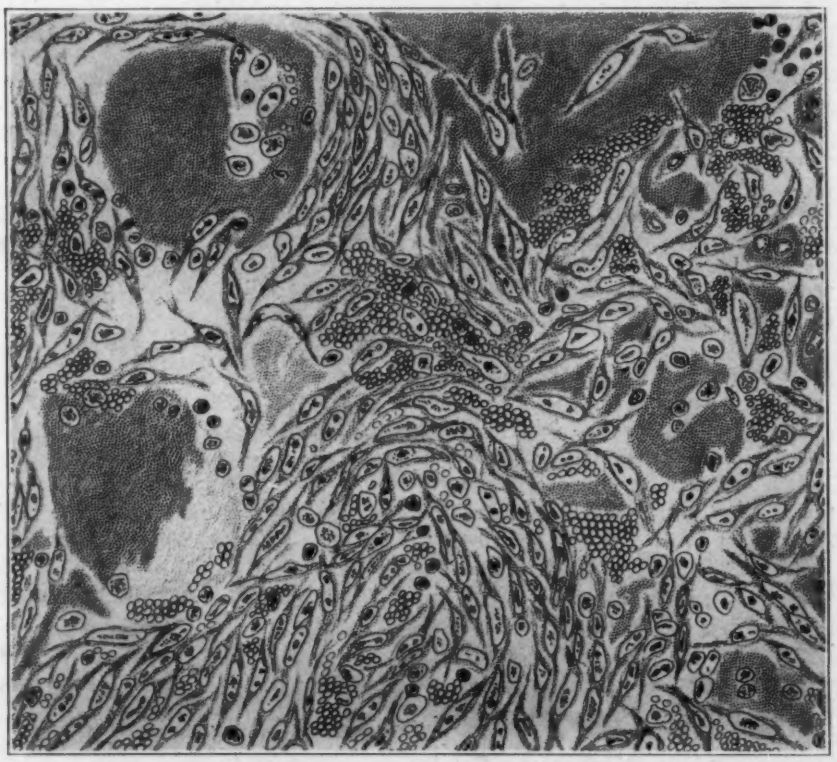

Fig. 3.—Section from dog thyroid removed eight days after injection with absolute alcohol (Dog 7).

The left thyroid lobe was exposed by the same procedure as used in Experiment 5. It measured 4 cm. by 2.5 cm. by 1.5 cm., and was of normal appearance and consistency. Three cubic centimeters of absolute alcohol was injected well into the gland substance, the needle being advanced from near the lower pole toward the superior one as the injection was made. The lobe became grayish, seared in appearance, edematous, more firm and increased in size. October 27, the wound was clean and healing. The dog was in good condition. The gland (left lobe) had returned to its size before injection. November 2, the wound had entirely healed. The wound was reopened, and the left lobe was removed.

The lobe was of the same size and appearance as before injection. There was, however, a definite hard area felt extending almost the entire length of the gland. On section, the region corresponding with the hard core presented a mottled appearance—pea size bluish-black material in a larger grayish zone. The border of the necrosed area was not sharply outlined. Apparently normal thyroid tissue extended into the area of necrosis in certain places. The surrounding thyroid tissue was apparently normal.

Microscopic examination revealed a relatively large central area of coagulation necrosis with thrombosis of the smaller vessels of the same region. There were small areas of hemorrhage through the area of necrosis. Along the border of the destroyed zone was cell proliferation and a moderate round cell infiltration. Bands of new fibroblasts extended into the area of necrosis along the blood vessels.

EXPERIMENT 8.—Dog 8, a healthy, large, all brown, long haired dog, in which the thyroid was not palpable, was operated on eight days after the injection of alcohol, Oct 25, 1923, under ether anesthesia, the same preparation as that given Dog 3 having been used.

The left thyroid lobe was exposed by the same procedure as that used in Experiment 5. This was 4.5 cm. by 2.5 cm. by 2 cm. in size, firm, elastic in consistency and of normal color. Four cubic centimeters of absolute alcohol was injected, beginning near the lower pole and progressing upward. The gland became enlarged by the volume of fluid introduced, and took on a grayish, cooked appearance over the injected region. The lobe was replaced, and the wound was closed. The dog remained in good condition. October 29, the wound showed two small superficial abscesses. The sutures of the region were removed. The left thyroid lobe, by palpation, was very hard, and was about one and one-half times the size observed before injection. November 3, the wound was entirely healed. The left lobe was not well made out by palpation. The left lobe was removed.

The lobe was the same size as before injection. There was a bluish-black coloration and a very definite general increase in firmness with parts that were very hard. The cut surface showed a mottled bluish-black and gray.

Microscopic examination revealed a large central area of coagulation necrosis with a small area of old hemorrhage. There was thrombosis and beginning organization of the smaller blood vessels of the area, and very marked fibroblastic proliferation about the blood vessels and surrounding the area of necrosis. The thyroid tissue surrounding this central coagulation necrosis was limited to a relatively thin strip.

EXPERIMENT 9.—Dog 9, a small, long haired poodle in only fair condition, was operated on eight days after the injection of alcohol, Dec. 19, 1923, under ether anesthesia, after the same preparation as that given Dog 5.

The right lobe was exposed by the usual method. The measurements were 2 cm. by 1.5 cm. by 1 cm. It was of normal appearance and consistency. Three cubic centimeters of absolute alcohol was injected. The entire gland became grayish and cooked in appearance. The volume of alcohol injected into this gland was very much greater in proportion to the size of the lobe than the amount used in the previous experiments. The lobe was replaced, and the wound was closed. December 23, the skin edges were separated in the lower half of the incision, and there was a moderate seropurulent discharge. December 27, the dog died during the night. The neck wound was gaping wide, and there was a large amount of blood in the cage.

There was extensive infection through the entire wound which involved the right thyroid lobe. There was sloughing of the lower pole, with rupture of the large vessels and hemorrhage.

On microscopic examination sections through the lower pole tissue that remained showed the wall of a phlegmon.

EXPERIMENT 10.—Dog 10, a long haired, black and white dog, showed definite fulness in the thyroid region; both lobes were distinctly felt, each being about the size of a hen's egg. Operation was performed eleven days after the injection of alcohol, Dec. 20, 1923, under ether anesthesia after preparation with soap and water, alcohol and tincture of iodin.

A No. 22 2-inch Luer needle was passed through the skin and intervening tissues into the right lobe of the thyroid. This lobe could be held between the thumb and the forefinger of the left hand. There was no bleeding from the needle. Eight cubic centimeters of absolute alcohol was injected, the position of the needle being changed from time to time during the procedure. The needle was withdrawn, and the puncture wound in the skin was sealed by a small cotton collodion dressing. December 23, to palpation, the right lobe was about one and one-half times the size before injection, and was very hard. There was moderate swelling of the soft tissues of the right neck. December 30, the swelling of the right neck had entirely subsided, and the right thyroid lobe, to palpation, was about the size of a hen's egg but much harder than before injection. December 31, the animal was killed, and the thyroid lobes were removed.

The two lobes were of about the same size. The left was of the appearance of normal thyroid tissue, grossly. The injected right lobe showed several pea-sized, bluish-black necrosed areas under the capsule. These were very hard and connected with a large, hard central core. On section, the cut surface of the gland showed a large amount of necrosis deep in the gland. The necrosis affected between one third and one half of the gland tissue.

Sections from the right lobe showed areas of coagulation necrosis which resembled those found in previous experiments on normal thyroids. There was round cell infiltration and fibroblastic proliferation similar in every respect to that described in Dog 8. The uninjected parts of the gland gave the picture of a diffuse colloid goiter with dilated acini filled with colloid and showing flattened acinous epithelium.

EXPERIMENT 11.—Dog 11, a light brown female, with a distemper-like cough, used because the only dog available at this time, was operated on twelve days after the injection of alcohol, Dec. 29, 1923, under ether anesthesia, after the same preparation as that given Dog 1.

The right thyroid lobe wa sexposed by the procedure used in Experiment 1. It was normal in consistency and appearance. Four cubic centimeters of absolute alcohol was injected into the deeper portion and throughout the entire length of the gland. The tissue became grayish, cooked and edematous in appearance. The lobe was replaced, and the wound was closed. December 31, the wound was clean. The dog was coughing a great deal. January 9, the wound was healed. The dog continued to cough, and the general condition was not good. January 10, the dog died during the night.

There was consolidation of the lower lobe of the right lung. The neck wound was clean throughout. The right lobe of the thyroid was removed for section. It was the size noted before injection, and much harder to palpation. The injected area was bluish-black.

The microscopic findings were those of coagulation necrosis with round cell infiltration and beginning fibrous tissue replacement.

EXPERIMENT 12.—Dog 12, a black and tan female, in good health, was operated on fourteen days after the injection of alcohol, Dec. 18, 1923, under ether anesthesia after the same preparation as that given Dog 1.

By the procedure used in Experiment 1, the right thyroid lobe was exposed. This measured 4.5 cm. by 3 cm. by 2.2 cm.; it was normal in appearance and firm and elastic to palpation. Three cubic centimeters of absolute alcohol was injected into the gland through a single puncture of the capsule. The gland took on a grayish, cooked appearance in the injected region. It was replaced, and the wound was closed. December 23, the wound was clean and healing well. The animal was in good condition. The right lobe felt somewhat larger than before injection and was very hard. December 27, the right lobe of the thyroid had decreased in size to about that found before injection. Jan. 2, 1924, the right lobe was removed. The measurements were 4.2 cm. by 2.8 cm. by 2.2 cm.

The gross and microscopic findings were similar to those found in Dog 11.

EXPERIMENT 13.—Dog 13 was a small, brown and white, short-haired dog, in good general condition, whose thyroid gland could not be felt. The dog was operated on fifteen days after the injection of alcohol, Dec. 18, 1923, under ether anesthesia after the same preparation as that given Dog 1.

The right thyroid lobe was exposed by the usual method. It was the size of an almond and normal in appearance and consistency. Two cubic centimeters of absolute alcohol was injected deep into the gland. The lobe became enlarged by the volume of fluid injected and took on a grayish, cooked appearance with bluish-black areas of coagulated blood showing through the capsule. The lobe was replaced, and the wound was closed. December 26, the wound was healed. The condition of the animal was good. Jan. 2, 1924, the right lobe was removed.

The gland was somewhat smaller than before injection. The color was bluish-black, evidently from old hemorrhage. On palpation, the lobe was very hard. The cut surface of the lobe near the center showed practically the entire gland as grayish and mottled in appearance, with smaller bluish areas of old hemorrhage.

Microscopic examination revealed a relatively large central area of coagulation necrosis with some smaller areas of hemorrhage. The boundary of the necrosis was very irregular, projections of normal thyroid tissue being almost entirely surounded by newly formed fibroblastic tissue. The peripheral thyroid tissue was normal in appearance, but was limited to a very narrow zone. There was a small amount of round cell infiltration about the border of the necrosis, and about the blood vessels that passed through the area. Fibroblastic proliferation was very marked about the periphery of the necrosis, and about the blood vessels. Heavy bands of newly formed fibrous tissue extended into the area of necrosis, both from the periphery and from the perivascular fibrous tissue.

EXPERIMENT 14.—Dog 14, a black and white, short-haired dog, in good condition, was operated on fifteen days after the injection of alcohol, Dec. 20, 1923, under ether anesthesia after the same preparation as that given Dog 1.

The right lobe was exposed. The measurements were 4 cm. by 2 cm. by 2 cm.; it was normal in color and consistency. Four cubic centimeters of absolute alcohol was injected from the lower pole upward. The gland tissue became grayish and seared in appearance in the injected region. The lobe was replaced, and the wound was closed. December 23, the right lobe was distinctly felt, and was about twice its previous size. It felt hard. The wound was clean.

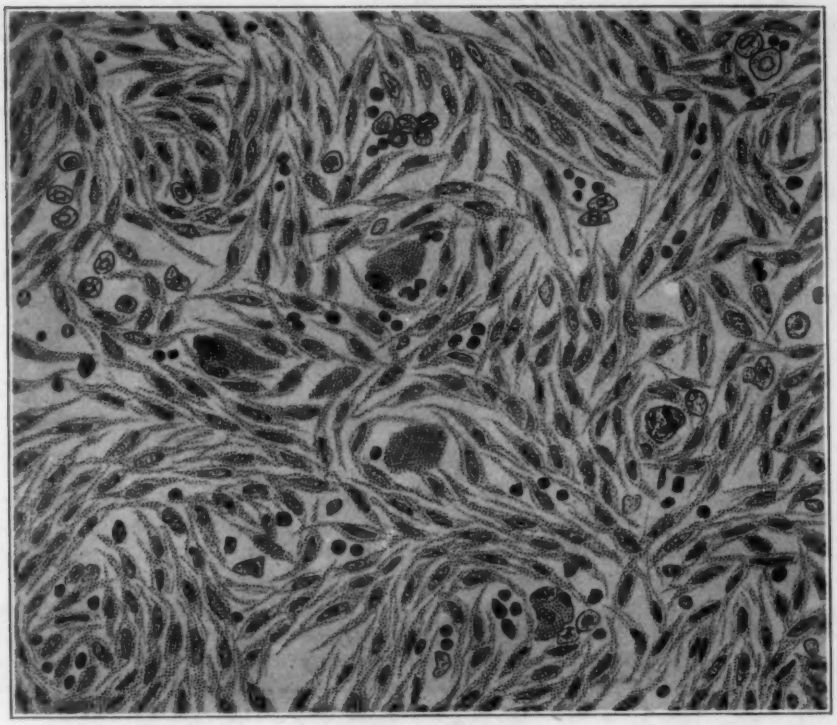

Fig. 4.—Section from thyroid removed fifteen days after injection with absolute alcohol (Dog 13).

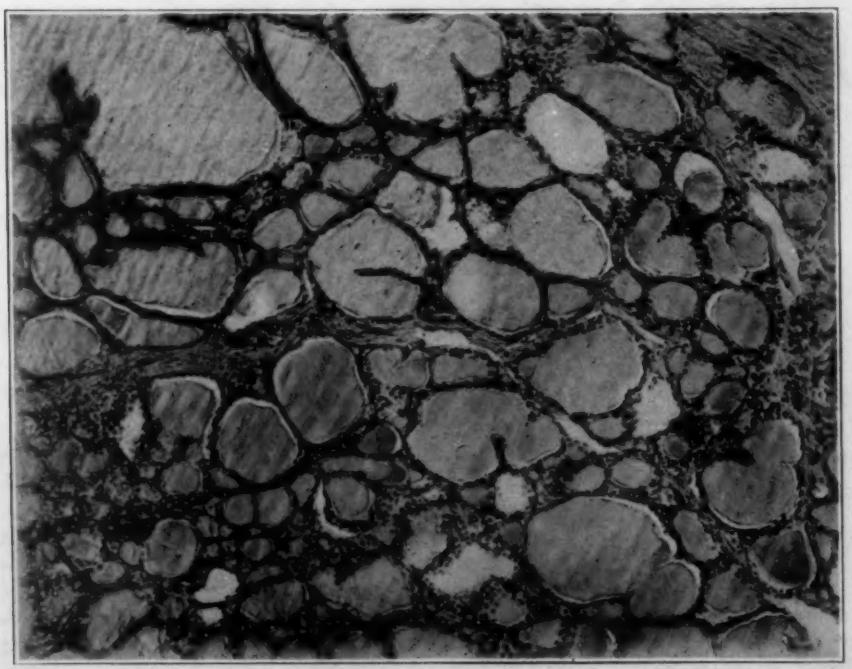

Fig. 5.—Low magnification photomicrograph of normal thyroid of dog.

December 30, the wound was healed. The right lobe had decreased markedly in size, and was not well made out by palpation. Jan. 5, 1924, the right thyroid lobe was removed.

There was no striking change in the size of the lobe. The color was darker than normal, a bluish-black in the injected region. On section, there was widespread necrosis with a zone of normal gland tissue making up the periphery of the lobe.

The microscopic examination revealed a condition similar to that in Dog 13, with patches of cloudy swelling in the more normal peripheral zone.

EXPERIMENT 15.—Dog 15 was a large white dog in good health. There was a definite fulness in the thyroid region, and each lobe, to palpation, was about the size of a lemon. They were smooth and firm, and did not have a cystic feel. Operation was performed forty seven days after the injection of alcohol, Jan. 15, 1924, under ether anesthesia following preparation by soap and water, alcohol and tincture of iodin.

The right lobe was picked up between the thumb and the fingers of the left hand. The No. 22 bore Luer needle was inserted through the skin and the intervening tissues into the thyroid. There was no bleeding. Ten cubic centimeters of absolute alcohol was injected, the needle being advanced from near the lower pole toward the upper pole during the injection. The animal's condition remained good. The needle was removed, and a small cotton collodion dressing was used to seal the puncture wound. January 18, there was moderate swelling of the right side in the neck region. The right lobe was moderately swollen and felt very hard. The general condition of the dog was good. January 20, the swelling of the neck and right lobe had subsided almost completely. February 15, the uninjected left lobe remained about the size of a lemon; the right was somewhat smaller than before injection and very much harder than the left. March 3, the left lobe remained about the size of a lemon; the right, to palpation, was about one-half the size of the left. The dog was killed, and both lobes were removed.

The measurements were: left lobe, 5.3 cm. by 3.1 cm. by 2.5 cm.; right lobe, 3 cm. by 1.9 cm. by 1.8 cm. The uninjected left lobe showed a smooth surface, firm, elastic in consistency and of a fresh, muscle-like color. The injected right lobe showed numerous pea-sized areas of scar contraction. The gland was hard, and had a darker color, as if from blood pigment. On section, there was a large amount of scar tissue through the deeper portion of the gland.

Sections through the hard central portion of the gland, on microscopic examination, showed masses of relatively new fibrous tissue with bands of the same tissue projecting into the adjacent thyroid tissue. There were bits of free colloid surrounded by foreign body giant cells. (The colloid acts as a foreign body after fixation by the alcohol.) The thyroid tissue of the periphery of the gland was not unlike that of the left lobe. There were islands of the thyroid tissue in the mass of connective tissue so surrounded that they would be expected to be destroyed when the fibrous tissue contracted.

EXPERIMENT 16.—Dog 16 was a medium sized dog in good condition. The thyroid lobes were palpable, but not greatly enlarged. To palpation, the two lobes were of equal size. Operation was done forty seven days after the injection of alcohol, Jan. 15, 1924, under ether anesthesia following preparation with soap and water, alcohol and tincture of iodin.

Subcutaneous injection was done as in Experiment 15. Five cubic centimeters of absolute alcohol was injected into the right lobe. The needle was advanced from near the lower toward the upper pole, as the injection was made. The

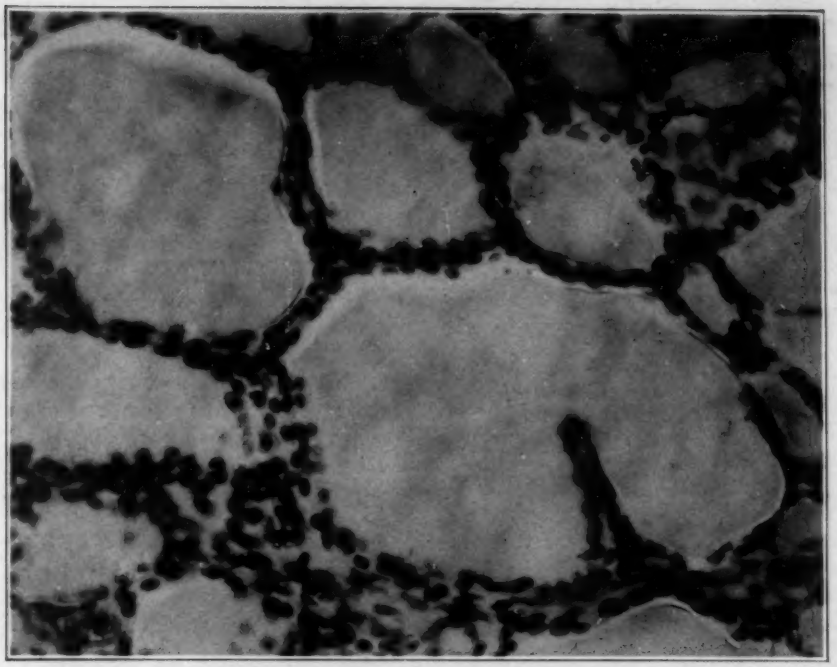

Fig. 6.—High magnification photomicrograph of normal thyroid of dog.

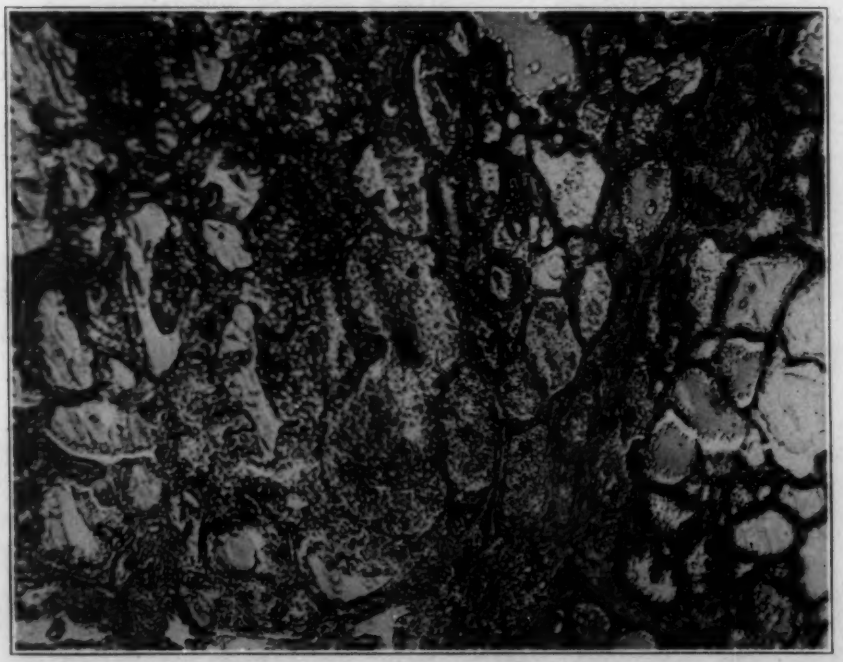

Fig. 7.—Low magnification photomicrograph of thyroid removed three days after injection (Dog 3).

puncture wound was closed with a cotton collodion dressing. January 25, the wound was completely healed. The general condition of the dog was good. The two thyroid lobes were felt, and were of about equal size. March 3, the right lobe of the thyroid was not distinctly felt—the left had not changed in size. The dog was killed, and both lobes of the thyroid removed.

The entire right lobe was dark brown and very hard. The measurements were: left lobe, 4.2 cm. by 2.3 cm. by 2 cm.; right lobe, 2.3 cm. by 1.2 cm. by 1 cm.

Through the center of sections, including an entire cross section of the gland, was seen a mass of dense fibrous tissue. In some sections, there were points at which the fibrous tissue extended to the gland capsule. Surrounding

Fig. 8.—High magnification photomicrograph of thyroid removed three days after injection (Dog 3).

this mass of connective tissue was normal thyroid tissue. Here and there through the new fibrous tissue, there were foreign body giant cells and round cell infiltration about small bits of colloid.

EXPERIMENT 17.—Dog 17, a large dog in good condition, in which the thyroid was not palpable, was operated on fifty-nine days after injection of alcohol, Jan. 11, 1924, under ether anesthesia following preparation with soap and water, alcohol and tincture of iodin.

The right thyroid was exposed as in Experiment 1. It measured 4.5 cm. by 2.2 cm. by 1.3 cm. Six cubic centimeters of absolute alcohol was injected deep into the gland. The lobe became gray and seared in appearance. It was replaced, and the wound was closed. January 25, the wound was healed, and the general condition of the animal was good. February 11, the right lobe was again exposed under ether anesthesia and aseptic conditions. It was somewhat

smaller than before injection, and, on palpation, a hard core was felt through its center. Five cubic centimeters of absolute alcohol was injected into the more normal appearing portion of the right lobe. The lobe was replaced, and the wound was closed. February 25, the wound had healed without infection. The dog was in good condition. March 11, the dog was killed, and both thyroid lobes were removed.

The right lobe was greatly decreased in size, showed areas of scar contraction and was lighter in color than normal thyroid tissue. The measurements were: left lobe, 4.5 cm. by 1.5 cm. by 1.1 cm.; right lobe, 1.3 cm. by 0.8 cm. by 0.5 cm.

The microscopic findings were similar to those in Dog 16. Cross sections through the entire gland showed a large central dense fibrous mass, with an

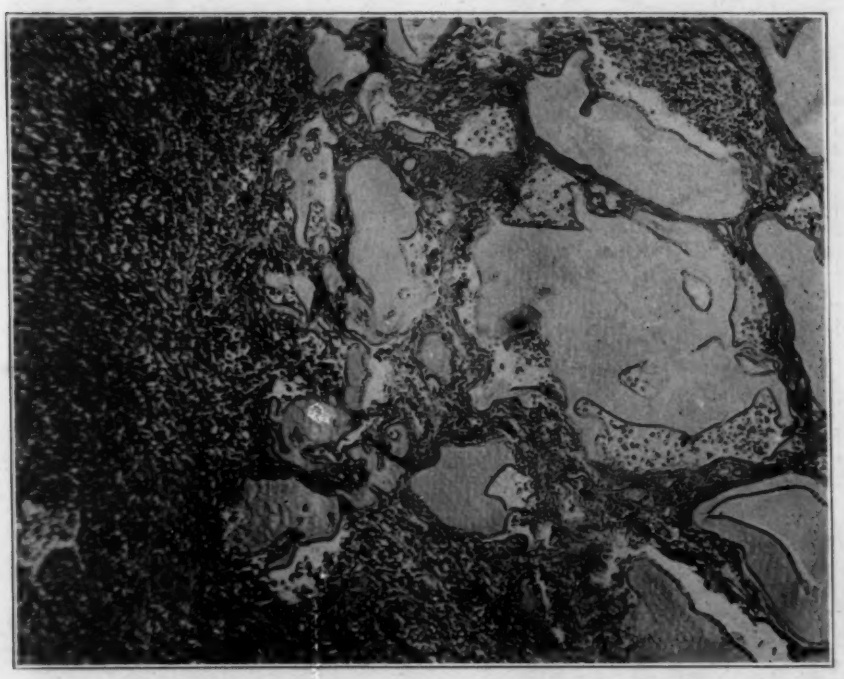

Fig. 9.—Low magnification photomicrograph of thyroid removed eleven days after injection (Dog 10).

incomplete, thin capsule of apparently normal thyroid tissue. There was practically no thyroid tissue or colloid material in the fibrous tissue mass, and only an occasional foreign body giant cell was found.

EXPERIMENT 18.—Dog 18, a medium sized dog in good health, was operated on fifty-nine days after the injection of alcohol, Jan. 11, 1924, under ether anesthesia following preparation with soap and water, alcohol and tincture of iodin.

The right thyroid lobe was exposed by the method used in Experiment 1. This measured 3.6 cm. by 1.8 cm. by 1 cm., and was approximately the size of the opposite lobe. Five cubic centimeters of absolute alcohol was injected, beginning at the inferior and extending to the superior pole. The gland became

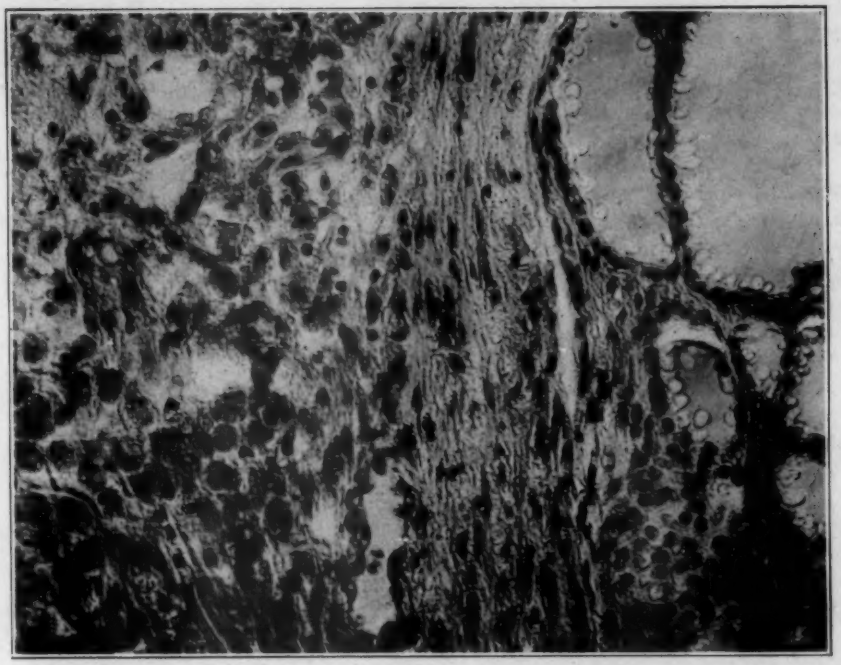

Fig. 10.—High magnification photomicrograph of thyroid removed eleven days after injection, showing fibroblastic proliferation in zone of destroyed thyroid tissue (Dog 10).

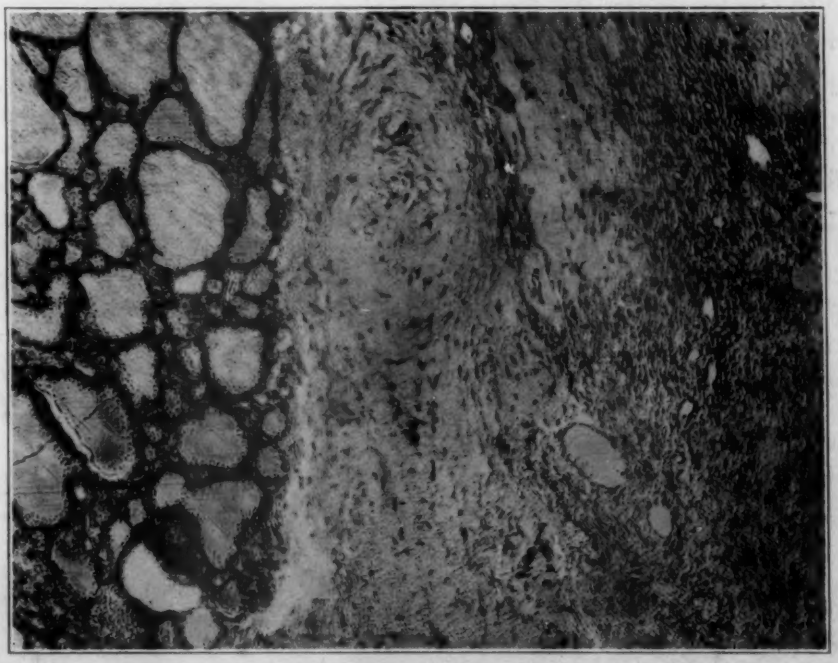

Fig. 11.—Thyroid fifty-nine days after injection, showing fibrous scar replacement of thyroid tissue (Dog 17).

gray and seared, with blotches of brown. The lobe was replaced, and the wound was closed. January 25, the wound had healed without infection. The animal was in good condition.

February 11, an operation similar to the first was performed. The right lobe was again exposed. The lower pole was very firm and bluish-black. A hard core extended upward, almost reaching the superior pole. The gland was about two-thirds its size before injection. Three cubic centimeters of absolute alcohol was injected into the more normal appearing portion of the lobe, and the lobe was replaced. The wound was closed. February 23, the wound had healed without infection. March 11, the dog was killed, and both lobes of thyroid were removed.

The right lobe was about half the size of the left. The left lobe was normal in appearance. The lower pole of the right lobe was dark brown, as from old hemorrhage. The upper half of the lobe was grayish-white. The entire lobe was very hard.

On microscopic examination, the right lobe was almost entirely replaced by scar tissue. At the periphery of the gland, small lobules of apparently normal thyroid tissue remained. Several sections included parathyroid tissue, which was normal in appearance. The detailed findings were similar to those in Dog 17.

COMMENT

The microscopic picture produced by the injection of absolute alcohol into the thyroid gland is that of coagulation necrosis in the area injected—the amount of necrosis being in direct proportion to the quantity of alcohol injected. This destruction is followed by round cell infiltration and very marked fibroblastic proliferation and infiltration. The colloid, after being acted on by the alcohol, acts as a foreign body, giving an even more active fibroblastic proliferation. Foreign body giant cells can be seen about bits of colloid in the older preparations. The ultimate picture is one of fibrous tissue replacement of the destroyed thyroid tissue.

In the process of infiltration of the alcohol from the immediate area of injection, it is evident from the material that this takes place chiefly in the perivascular tissues. Since the sympathetic fibers course in this perivascular tissue and can be seen in sections, it is to be expected that they are destroyed in a larger area of gland tissue than that involved by the alcohol. Special stains have not been made, however, to determine this point. The blood vessels passing through the area of infiltration show thrombosis and, in the older experiments, organization and canalization. In large injections, this in itself must mean a considerable decrease in blood supply for the gland as a whole.

In the older experiments, sections showed small nests of fairly normal acini surrounded by a mass of new fibrous tissue. With a later stage and contraction of the fibrous tissue, these secreting cells would undoubtedly be destroyed. Porter has pointed out that this strangulation of islands of active thyroid tissue by fibrous tissue contraction

probably accounts for the continued improvement for several weeks after boiling water injections in toxic goiter cases.

There was no immediate or delayed general effect from the alcohol in these experiments. Ten cubic centimeters was the largest quantity used at one sitting, but this is probably as large a quantity as would be required for a single injection in a human being. From the experimental results of Hyatt [25] and others,[26] it is not to be expected that the quantity of alcohol necessary for thyroid injection purposes would have any effect on pulse, respiration or blood pressure.

The ease with which alcohol can be injected and the harmlessness of the procedure suggests the use of this solution for destruction of thyroid gland tissue as a preliminary preparatory measure. The process of destruction resembles that produced by the injection of boiling water but is accomplished without the inconveniences and without special apparatus.

CONCLUSIONS

1. Alcohol injected into the thyroid gland produces a local coagulation necrosis. The extent of gland destruction is in direct proportion to the amount of alcohol injected. Thus, by repeated injections, the active gland tissue may be reduced to the amount desired.

2. With the amount of alcohol necessary for practical purposes there is no general effect.

3. The microscopic picture after absolute alcohol injection is similar to that produced by boiling water.

4. Alcohol injections can be made without the inconveniences and difficulties that are unavoidable with boiling water injections.

5. These experiments warrant the conclusion that the injection of absolute alcohol in suitable quantity in cases of thyroid disease in which the use of boiling water has been suggested and used is a safe and legitimate method and is recommended as an operative procedure in thyroid surgery.

Clinical cases of toxic goiter in which absolute alcohol injection of the thyroid gland is being done are under observation.

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25. Hyatt, E G.: Action of Alcohol on the Heart and Respiration, J. Lab. & Clin. Med. **5**:56 (Oct.) 1919.

26. Wallace, G. B.: Some Considerations of the Pharmacology and Therapeutic Value of Alcohol, M. Rec. **101**:47 (Jan. 14) 1922. Engelen, P.: Einfluss des Alkohols auf Herzenhythmien, Zentralbl. f. inn. Med. **42**:857 (Nov. 5) 1921; Puls druckmessungen nach Alkoholaufnahme, ibid. **42**:570 (July 16) 1921.

DYSPNEA FOLLOWING THYROID OPERATIONS*

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The mortality in thyroid operations during the last fifty years has decreased so extensively that in nontoxic goiters it is almost negligible, while in the toxic types it is only from 2 to 5 per cent. Various factors have brought about these reductions. Owing to the invention of the artery clamp by Paeon [1] and the researches of Streckeisen [2] and Kocher [3] on the blood supply of the thyroid gland, hemorrhage has been removed as the prime cause of death. Rose [4] called attention to the importance of tracheal compression, and the possibility of asphyxia due to tracheal obstruction. The rôle of recurrent laryngeal nerve injury as a possible contributory cause of death was emphasized by Seitz.[5] Today, the earlier operation, the better preoperative preparation, the use of gas and oxygen and of local anesthesia, the improved operative technic and the important changes in after-treatment have aided greatly in diminishing the mortality. And yet, in spite of all these precautions, there is an occasional death and surgery receives but little credit for its 95 per cent. of operative recoveries, but severe censure for its 5 per cent. of deaths.

The picture of thyrotoxic death is now so universally recognized that it does not concern us here. We are interested in those conditions in which a patient, either during or in the first twenty hours after operation, becomes progressively cyanotic and increasingly dyspneic, often to such a degree that death results from asphyxia. The explanation of this particular picture should not be difficult, and yet, on closer analysis, there are many factors which cannot be properly correlated, many findings which are paradoxic, and experimental data which partially refute certain definite clinical findings. It is not a simple problem. To be sure, the cause of this asphyxia might theoretically be a disturbance in the nervous mechanism of the larynx, edema of the glottis, pathologic changes in the general architecture of the trachea, a combination of a laryngeal plus tracheal obstruction, or possibly some cause not connected with the upper respiratory passage, but connected with the cardiovascular system.

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* From the Laboratory of Surgical Research, Columbia University College of Physicians and Surgeons.

1. Paeon, cited by Halsted: Story of Goiter, Rep. Johns Hopkins Hosp. **19**:189.
2. Streckeisen: Virchows Arch. f. path. Anat. **103**:131, 1886.
3. Grützner, cited by Kocher: Arch. f. klin. Chir. **29**:254, 1883.
4. Rose: Arch. f. klin. Chir. **22**, No. 1, 1878.
5. Seitz: Arch. f. klin. Chir. **29**:146, 1883.

To determine the rôle of the recurrent laryngeal nerves and of the trachea as factors in sudden thyroid deaths, an attempt was made first to find what evidence animal experimentation might reveal, and, second, to review clinical statistics from the early thyroid clinics bearing on these anatomic structures.

The anatomy of the recurrent laryngeal nerves is of great importance surgically because these nerves are liable to injury in ligation of the thyroid arteries and veins. According to Gray,[6] the left one arises in front of the arch of the aorta and, winding from before backward, ascends to the side of the trachea. The right is derived anterior to the subclavian artery and, coursing from there backward around that vessel, ascends obliquely to the right side of the trachea behind the common carotid, either in front or behind the inferior thyroid artery. The nerve on each side ascends in the groove between the trachea and the esophagus and, passing under the lower border of the inferior constrictor muscle, enters the larynx behind the articulation of the inferior cornu of the thyroid cartilage with the cricoid and is distributed to all the intrinsic muscles of the larynx excepting those comprising the ventricular bands, aryepiglottic folds and the cricothyroid. This muscle is supplied by the superior laryngeal nerve and raises the cricoid on the thyroid, producing longitudinal tension of the vocal cords. The recurrent laryngeal nerve, then, supplies those muscles which close and open the glottis. The closers of the glottis, the adductors, are the internal thyro-arytenoids, the lateral cricoarytenoids and the transverse muscles, inactive during respiration, and only active when phonation is required. For sound production, the vocal cords are brought into apposition in the median line of the glottis by an autonomic coordination of muscular action. The openers of the glottis, the abductors, are the posterior cricoarytenoids. These have nothing to do with phonation, but are continually active in respiration, holding the glottis open for the entrance and the exit of air. The recurrent laryngeal nerve, then, carries fibers, one group of which causes adduction, the other group abduction of the vocal cords. Schech [7] was able to trace these different sets of fibers to the individual laryngeal muscles and by stimulation of the individual bundles to open and close the glottis at will. Direct stimulation of the nerves directly causes a dilatation of the glottis in some animals, closes it in others and may produce both effects in the same animal.

In a series of experiments on the effect of stimulation of the recurrent laryngeal nerves of dogs under anesthesia with varying degrees of the faradic current, our results were analogous to those obtained by Hooper.[8]

6. Gray: Anatomy, Spitzka, 1910.
7. Schech: Wurzburg, Habilitationschrift, 1873.
8. Hooper: New York M. J., July, 1887.

The larynx was examined by means of a Brown-Buerger urethroscope, which because of its convenient size gave an excellent view of the interior of the larynx and could be passed without difficulty into the lower portion of the trachea. When the animal was under deep ether anesthesia there was an abduction of the cords, with no response to stimulation of the recurrent nerve. Stimulation of the nerves when the animal was under lighter narcosis caused a complete dilatation, the vocal processes of the arytenoid cartilages were turned outward, and a large opening was maintained during the time stimulation was continued. As the narcosis became less, a series of mixed movements took place, that is, there was an opening of the posterior portion of the cords with a contraction of the ligamentous portion in front, giving the glottis a rhomboidal appearance. But, as the current was increased, the cords became adducted, and this position was produced by decreasing stimulation as the dog regained consciousness. When the cords were in adduction, there was always a small chink between them and though they were held in this position at will for varying lengths of time by stimulation, at no period was the respiration of the animal embarrassed.

If the inferior laryngeal nerves of the dogs were cut, the cords assumed the cadaveric position. They lost their bark, there was some difficulty in deglutition, and the dyspnea which was present became quite marked, especially when any undue exertion was indulged in. Schech, by forcing his dogs to exercise, caused their death by asphyxia. Judd [9] believes that this obstructive dyspnea results because there is a tendency of the paralyzed cords to be sucked inward on inspiration and form pockets laterally, which may act as valves and, in extreme cases, completely shut off the air. These animals are quite miserable, the accessory muscles of respiration are continually used, and the entire shape of the thorax may be changed. This picture is quite different from the one observed in man. Here dyspnea of such magnitude is a late complication.

However, these dogs took the anesthetic fairly well, and at no time during or following the various operative procedures to which they were subjected did any of them die or show increased dyspnea. Frey [10] has stated that immediate death in a dog from double inferior laryngeal nerve section has never been reported.

Remembering that the abductor fibers run in distinct bundles along the mesial aspect of the nerve, an attempt was made to cause a wide opening of the glottis by focal stimulation when the dogs were under light anesthesia. The effect was the same as when the entire nerve was stimulated. In an attempt to destroy the abductor fibers, the mesial aspect of the nerve was crushed with a mosquito artery clamp. This was

9. Judd, E. S.: Ann. Surg. **67**:257 (March) 1918.
10. Frey: Pathologische Lungenveranderungen, 1887.

unsuccessful. As a matter of fact, the only results obtained when any pressure was exerted on the recurrent laryngeal nerves was a paralysis of the vocal cord of the corresponding side. These findings were previously reported by Judd and New in a large series of dogs.

As the majority of goiter cases are complicated by varying degrees of tracheal compression, it was thought death or severe obstructive dyspnea might be produced were the insult of recurrent laryngeal nerve injury added to artifically produced tracheal stenoses. The method of producing this tracheal narrowing was different from that in thyroid disease, but the end-result was practically the same. Normal dogs were anesthetized, and varying numbers of the tracheal cartilaginous rings were excised subperichondrially. By careful dissection, the underlying mucous membrane remained intact.

If from one to three rings were removed almost completely, the caliber of the underlying tube of mucous membrane remained practically normal, and nothing unusual was noted. The intact rings above and below the resected ones, and the normal, longitudinal tension of the trachea were apparently sufficient to overcome the suction action of the inspired air. It was possible, in some dogs, to remove seven rings without the least inspiratory stridor resulting, although there was a slight lateral inspiratory collapse of the tracheal mucous membrane. If more cartilages were removed, there was inspiratory infolding of the mucous membrane which varied directly with the number of rings excised. On only one occasion after removing about one third of the entire length of the cartilaginous support of the trachea was there a real "tracheal collapse." There was a progressively increasing inspiratory stridor which would have resulted in death had not a whalebone catheter been inserted through the larynx, affording a rigid air passage.

If, in excising the tracheal rings, the mucous membrane of the trachea was incised, the animal became dyspneic immediately and there was marked inspiratory stridor, with an increase in the extent of collapse of the tracheal wall. A suture introduced to close the perforation rapidly relieved these symptoms. When the interior of the trachea was observed with the urethroscope, its collapse could be seen with each inspiration. But, within a few days, there was definite fixation of this area with encroachment on the lumen of the trachea. If these dogs were operated on subsequently and the overlying ribbon muscles carefully dissected from the stenosed trachea, there was no recurrence of the inspiratory tracheal collapse. The scar tissue seemed of sufficient strength to support adequately the mucous membrane. These animals with moderately stenosed tracheas took anesthesia as well as human beings with a moderate degree of tracheal compression. As time passed, subsequent tracheoscopies revealed a diminution of the tracheal stricture which can

be accounted for by the persistent dilating effect of the inspired air on a tube without external pressure and the adherence of the trachea to the ribbon muscles.

When the recurrent laryngeal nerves were stimulated with varying degrees of the faradic current during light anesthesia, dyspnea at no time resulted, and dogs with a double vocal cord paralysis on whom a tracheal stenosis had been produced never died during or soon after the operation.

The results obtained were especially interesting so far as the term "tracheal collapse" is concerned. Tracheal collapse does occur clinically. Anyone who has seen this terrifying surgical complication does not doubt its reality, but it is and must be a surgical rarity. As a cause of operative death in exophthalmic goiter, it probably never occurs. Actual collapse of a tracheal tube is unusual because of its architecture. The trachea is held open by the regular interposition of cartilaginous rings, and even if several of the intermediary rings have been partially or completely destroyed, those above and below are invariably capable of maintaining a lumen sufficient for respiratory needs.

A glance at the exhibits of compressed and deviated tracheas of Demme [11] and Wild [12] will convince the most skeptical that the margin of safety must be extremely large. Lumina reduced to transverse slits and S-shaped tubes are not only compatible with life, but, under normal conditions of stress and strain, such patients get along fairly well and are moderately comfortable. Thyroid enlargements cause a great many tracheal deviations with changes in, and destructions of, the cartilages. The tumor mass itself may act as a support for the weakened wall. If after the removal of the thyroid, the underlying scar tissue is insufficient, the suction action of the inspired air may be great enough to cause a collapse of the trachea. This rarely happens and accounts for only an unusually small percentage of deaths from obstructive dyspnea. There are, however, two other contributory factors in tracheal obstruction. Thick, tenacious mucus, and congestion and swelling of the mucosa, the result of operative trauma or ether anesthesia, may so obstruct the trachea as to call for an immediate tracheotomy. Furthermore, Grützner,[3] a worker in Kocher's clinic, in a study of necropsy material from compressed tracheas, showed that the ciliated epithelium of the mucous membrane, in this particular region, was altered. Owing to the absence of ciliary action, the accumulating mucus may not be efficiently propelled along the trachea.[13]

What part the vocal cords play in thyroid dyspnea is still open to much discussion. Injuries to the recurrent laryngeal nerves during

11. Demme: Wurzb. med. Ztschr. **3**:254, 1892.
12. Wild: Beitr. z. klin. Chir. **45**, No. 1, 1905.
13. Simmonds: Virchows Arch. f. path. Anat. **179**:15, 1905.

thyroidectomy, while not as frequent as formerly, are by no means rare. According to Crotti,[14] these lesions are "relatively frequent, of slight importance, varying from 7 to 35 per cent." The frequency of their occurrence varies directly with the conscientiousness with which routine postoperative laryngoscopic examinations are made.

Traumatization of one nerve, while resulting in a paralysis of the corresponding vocal cord, may give but few symptoms clinically. The voice may not even be noticeably changed, and dyspnea may be entirely absent. Nor is hoarseness always evidence that there has been an interference with cord function.[15] The exact positions assumed by the vocal bands after recurrent paralysis have been the cause of much discussion. There are so many factors concerned in the proper interpretation of the laryngoscopic picture that numerous opinions have been given. Theoretically, in complete paralysis, the position of the cord should be intermediate, yet, clinically, Pemberton[16] states that "injury of the nerve, such as is inflicted by suturing, clamping or severing, results in a paralysis of the vocal cord, which is usually manifested by complete abductor paralysis so that the cord lies in the midline position, thereby narrowing the glottis. Occasionally, however, it is found in the intermediate or cadaveric position. Injury to both nerves is followed by early obstructive dyspnea." Only the median position of a cord would result seriously, as the lumen for inspired air is immediately shut off by about one-half. Yet, this alone should not produce fatal dyspnea, for patients intubated with the O'Dwyer tube with its narrow lumen receive sufficient air space; and innumerable patients from one cause or another suffering from sudden unilateral abductor paralysis do not show much, if any, dyspnea. If, however, from previous pressure of a thyroid tumor, an abductor paralysis has caused the median position of one cord, any nerve injury resulting in a limitation of movement of the other might so narrow the glottis that serious obstructive dyspnea would easily result.

Semon[17] first drew attention to the fact that the abductor fibers of the recurrent laryngeal nerve become involved sooner than the adductors, not only in lesions of the nerves, but also in cases of undoubted cerebral injury, and he was able to prove his assertion by compiling twenty-two cases from the literature. Paralysis of the abductors at first simply results in the cords being pulled to the cadaveric position. Dyspnea, in the beginning, is not marked, and phonation is normal. However, later,

14. Crotti: Thyroid and Thymus, Ed. 2, Philadelphia, Lea & Febiger, 1922.
15. Amersbach: Ztschr. f. Heilk. **6**, No. 7, 1923.
16. Pemberton, J. de J.: S. Clin. N. A. **4**:451 (April) 1924.
17. Semon: Tr. Clin. Soc. **12**:189, 1879; Arch. f. Laryngol. u. Rhinol. **2**, No. 3, July, 1881.

there probably is a paralytic contracture of the antagonists, with the result that there is a slow, gradual, irresistible narrowing of the vocal cords from the intermediate position to touching in the midline.[18]

Complete division of the recurrent laryngeal nerves on both sides results presumably in a cadaveric position of the vocal cords, a marked impairment of voice and dyspnea, especially on exertion, because, while the vocal cords in the intermediate position leave sufficient space for the needs of ordinary quiet respiration, the caliber of the narrowed glottis does not permit sufficient entrance of air for the demand of any strenuous exertion. If the median position of the cords was the usual occurrence, death should result immediately, but recorded cases of double recurrent paralysis bear witness to the fact that this is not so. The subsequent course of these unfortunate patients is exceedingly distressing, because, in the majority, there is a tendency for this dyspnea to increase so much that, unless there is immediate surgical intervention, death from asphyxia may occur. However, this is usually a late result, and it is due to the fact that as time goes on the cords are drawn nearer and nearer the median line, and to compensate for the narrowed glottis there is a compensatory lengthening of the period of inspiration with stridor and a development of the accessory muscles of respiration.

In a series of 191 cases of thyroid disease operated on by Krönlein,[19] there were none which did not have thyroid dyspnea, some of the patients being awakened out of sleep with severe signs of asphyxia. Forty-nine of these cases presented disturbance of the vocal cords, and seven showed a unilateral cord paralysis. Forty-two of sixty-two patients who had attacks of suffocation revealed no disturbance of their vocal cords. And of the forty-nine with changes, twenty had attacks of suffocation. Of the seven with unilateral paralysis, four had suffocation attacks. Certainly, these statistics indicate definitely that attacks of suffocation after, as well as before, operation may occur without any vocal cord disturbances, and that the two conditions are not necessarily related. Krönlein believes that the cause of sudden suffocation either before or after thyroid operations is obscure. It apparently does not depend on injuries to nerve supply of the glottis, resulting either in a paralysis of the glottis openers, or a spasm of the glottis closers. Certainly, this oxygen insufficiency leading to asphyxia may arise from causes other than those present either in the larynx or the trachea.

In some nontoxic and certainly in most toxic thyroids, the heart is another important element which must be borne constantly in mind. The goiter heart has always been the center of much interest. In a

18. Rosenbach: Breslauer artz. Ztschr., No. 2, July 24, 1880.
19. Krönlein: Beitr. z. klin. Chir. 9:577, 1892.

series of patients from the third to the sixth decade with endemic goiter, quoted by Coller,[20] the average number with tracheal pressure was about 25 per cent., and those with enlarged hearts about 39 per cent. The number of patients with cardiac enlargement, tachycardia and cardiac irregularities definitely increased with the succeeding decades of life. De Quervain,[21] in a study of simple goiter in 1,682 patients, reported one postoperative death in those under 40 years of age, but over 40, the time of life when cardiovascular and renal manifestations appear, there was an increase in mortality from 1 per cent. between the fourth and fifth decade to 25 per cent. between the eighth and ninth decades. It is a well known fact that patients with exophthalmic goiter stand abdominal operation poorly. This is dependent, in many instances, on their impaired cardiac condition. This was emphasized many years ago by Hirst.[22] Wilson [23] states that while symptoms of dyspnea and cardiorespiratory weakness may be produced in normal persons by sufficiently strenuous exercise, the same may be caused in patients with toxic goiter by even moderate exertion. All toxic goiters are actually or potentially cardiac with a respiratory rate which is higher than normal. There is no doubt that, in recovering from an anesthetic, the restlessness and the purposeless movements that are made require more than the ordinary amount of oxygen, and if this is not supplied, for one reason or another, dyspnea may occur.

There are many cases of abdominal operations which postoperatively soon develop increasing cyanosis and dyspnea, occasionally terminating fatally. Had the same picture developed after a thyroid operation, an emergency tracheotomy would have been performed immediately. However, it is easy to conceive that anything which will curtail the air intake, especially in thyroid cardiac patients whose demand for oxygen is more than the average, might result in dyspnea. Tracheotomy may help only those cases in which the dyspnea is due to obstruction, but there are others which tracheotomy does not help and which, at necropsy, disclose a normal larynx and trachea and intact inferior laryngeal nerves. In the last group of cases, the cause of dyspnea and ensuing death is still obscure.

SUMMARY

1. Following thyroidectomy, sudden death characterized by the sudden development of marked cyanosis and dyspnea may occur. This

20. Coller, F. A.: Morbidity of Endemic Goiter, J. A. M. A. **82**:1745 (May 31) 1924,

21. Quervain, F.: Presse méd. **32**:69 (Jan. 23) 1924.

22. Hirst: M. Rec. **68**, 1905.

23. Wilson, F. N.: Cardiac Disturbances Associated with Diseases of Thyroid Gland, J. A. M. A. **82**:1754 (May 31) 1924.

accident occurs in most instances within twenty-four hours after operation. It is not associated with signs of thyrotoxicosis or any premonitory symptoms that would lead one to suspect a fatal issue. It has been attributed by various writers to tracheal collapse or injury to the nerve supply of the larynx.

2. Experimentally, tracheomalacia may be simulated by the resection of tracheal cartilages. In dogs, as many as seven tracheal rings can be excised without causing appreciable collapse of the tracheal wall. More extensive resection resulted in an inspiratory infolding of the tracheal mucosa with the development of inspiratory stridor.

3. The effect of stimulation of the recurrent laryngeal nerves on the movements of the vocal cords of an anesthetized dog depends on the depth of the anesthesia. Under deep narcosis, there was no response. Under moderate anesthesia, the cords were abducted. As the animal was recovering from the anesthetic state, the posterior portions of the glottis were abducted and the anterior parts adducted, and finally complete adduction occurred.

4. Section of both recurrent laryngeal nerves in dogs caused the cords to assume the cadaveric position. These dogs lost their bark. They took the anesthetic without difficulty.

5. Section of both recurrent laryngeal nerves in dogs combined with resection of tracheal cartilages to produce tracheal stenosis did not cause the death of the dogs. Similarly, stimulation of both recurrent laryngeal nerves in dogs in which trachael stenosis had been produced was not fatal.

6. From an experimental basis, fatal dyspnea following thyroidectomy does not seem to be due directly to nerve injury, tracheal stenosis or both factors combined. It is more likely due to a combination of circumstances from which the possibility of cardiorespiratory collapse connot be excluded.

PROTOCOLS

EXPERIMENT 1.—Dog 1 was placed under ether anesthesia, Feb. 1, 1924. A midline incision was made; the muscles were separated and the trachea was exposed. The two inferior laryngeal nerves were isolated and stimulated with varying degrees of the faradic current under deep and light anesthesia, singly and together. During this procedure, the larynx was examined with a Brown-Berger urethroscope. Under deep anesthesia, both cords were abducted, and stimulation had no effect. As the anesthesia became lighter, the strong faradic current caused further abduction under the cords. With lighter anesthesia and a strong current, the ligamentous portions of the cord were brought into proximity, while the posterior part still remained in abduction, giving the glottis a rhomboidal appearance. This was originally designated by Hooper as "mixed movement." As the anesthesia became very light, stimulation with very weak current produced adduction. Although the adducted position was maintained for varying lengths

of time, a small oblong chink always remained between the cords, and at no time was there any dyspnea or interference with respiration. Just below the cricoid cartilage, two cartilaginous rings of the trachea were removed subperichondrally. Practically no alteration in the caliber of the trachea was noted, and a very slight inspiratory collapse was evident.

February 8, a tracheoscopy under ether anesthesia was done. The cords were normal. The diameter of the trachea appeared only slightly constricted at the site of the operation.

February 11, an examination gave the same findings as on February 8.

Fig. 1.—Specimens in Experiment 1.

March 7, a tracheoscopy was done under ether anesthesia; the cords moved normally, and there was slight stenosis of the trachea at the site of operation.

March 14, an examination gave the same results as the previous one. March 21, there was no change.

April 22, a tracheoscopy under ether anesthesia showed the movements of the cords to be normal. The trachea was practically normal in caliber.

May 2, under ether anesthesia, the midline incision in the neck was reincised. The trachea was exposed, and slight constriction just below the cricoid cartilage was noted. A piece of the entire tracheal wall, about 1 cm. square, was excised,

and the opening completely closed with three interrupted silk sutures. A good closure, air-tight, was effected. After this procedure, the animal breathed well and was not dyspneic. The two recurrent laryngeal nerves were isolated and stimulated with varying degrees of the faradic current, singly and together, under deep and light anesthesia, without any dyspnea or respiratory embarrassment resulting. Both nerves were ligated with silk, with the result that the cords became motionless and occupied the cadaveric position. Closure was made in layers.

May 15, the dog was dyspneic. Dyspnea was increased on exertion. There was definite interference with deglutition, and the bark was apparently lost.

Fig. 2.—Specimens in Experiment 2.

Tracheoscopy was done under ether anesthesia. The cords were in the cadaveric position, sucked in slightly with inspiration, but they returned to their abducted position with expiration. There was extensive collapse of the tracheal wall in the region of the operation. Stridor and dyspnea were noted.

November 15, the dog was killed with chloroform. There was tracheal deformity as shown in Figure 1.

EXPERIMENT 2.—Dog 2 was placed under ether anesthesia, Feb. 1, 1924, and a midline incision was made in the neck; the muscles were separated, and the trachea was exposed. Both laryngeal nerves (inferior) were isolated and the nerves were stimulated with varying degrees of faradic current, the interior of

the larynx being examined at the same time with the urethroscope. At first, there was complete dilatation, and then, as the anesthesia was removed, mixed movements became apparent with gradual adduction of the vocal cords, with a very weak current, as the dog regained consciousness. The anesthetic was resumed, and, just below the cricoid cartilage, three tracheal rings were excised at their posterior attachment. There was very little alteration in the caliber of the trachea, although there was a very slight inspiratory collapse. The latter was only apparent after the third ring was removed. Skin and muscle were sutured interruptedly.

Fig. 3.—Specimens in Experiment 3.

February 8, the dog was quite comfortable, and, under anesthesia, the vocal cords when examined appeared normal, as did the diameter of the trachea.

February 11, there was a very mild degree of tracheal stenosis.

March 7, there was no evidence of tracheal stenosis.

March 17, the dog died during the night. Examination of the trachea showed no diminution in the caliber of the lumen in the region where the three rings had been excised.

EXPERIMENT 3.—Dog 3 was placed under ether anesthesia, Feb. 8, 1924, and a midline incision made in the neck; the muscles were separated and the trachea was exposed. Both inferior laryngeal nerves were isolated and stimulated with

varying degrees of faradic current; the interior of the larynx was examined at the same time with the urethroscope. Each nerve was stimulated separately, and then both together. At first, there was complete dilatation of the vocal cords, and then, as the anesthetic was removed, mixed movements were present with gradual adduction of the vocal cords, with a very weak current, as the dog regained consciousness. The anesthetic was resumed, and five rings were removed subperichondrially in the midregion of the trachea. Slight inspiratory collapse of the mucous membrane was noted. Suture of skin and muscles was done.

Fig. 4.—Specimens in Experiment 4.

February 11, the dog was comfortable. Under anesthesia, the trachea was examined with a urethroscope. There was no apparent stenosis of the trachea.

February 18, the dog succumbed from distemper. The trachea, above and below the point where the rings were removed, was normal. In this area, there was a very definite transverse narrowing of the trachea, although there was sufficient space, at least 7 mm. in diameter, from before backward. The recurrent laryngeal nerves were normal.

EXPERIMENT 4.—Dog 4 was placed under ether anesthesia, Feb. 8, 1924, and a midline incision made in the neck; the muscles were separated, and the trachea was exposed. Both inferior laryngeal nerves were isolated and stimulated with

varying degrees of the faradic current, under light and deep anesthesia. The interior of the larynx was examined with the urethroscope, and the results obtained were similar to those in Experiment 3. The recurrent laryngeal nerve on one side was partially cut through the mesial portion, and the other nerve was ligated with catgut. Both cords were in a cadaveric position without motion.

February 11, the dog was dyspneic, and the condition was increased especially when the animal ate. There appeared to be difficulty in deglutition. The bark was lost. Tracheoscopy was done under ether anesthesia. The cords were in the cadaveric position, thickened and edematous, with practically no motion during respiration.

March 14, tracheoscopy was done, under ether anesthesia. The appearance was the same as that noted, February 11. The animal had lost weight.

March 21, tracheoscopy was done, under ether anesthesia. The appearance of the cord was practically the same. The animal appeared more emaciated and generally miserable. There was a slight change in the general appearance of the thorax; it seemed narrowed from side to side.

March 28, under ether anesthesia, a midline incision was made in the neck; the muscles were separated, and the trachea was carefully exposed. The fourth tracheal ring was removed completely. From the seventh ring down and for about ten cartilages, the tracheal rings were completely removed for one-half their extent. Although there was definite inspiratory collapse of the left half of the tracheal mucous membrane, there was no stridor, nor was there any interference with respiration except when a small perforation was accidentally made. The mucous membrane collapsed more, and definite stridor developed. Suture of this perforation immediately remedied the condition; the collapse diminished, and the stridor disappeared. At no time, however, was there very marked asphyxia or definite interference with respiration. Closure was made in layers.

April 5, the animal had lost more weight. The dyspnea had not increased materially. Marked stridor was noticed when the animal was asleep in his kennel, but was not apparent when the animal was up and about.

April 22, tracheoscopy was done, under ether anesthesia. The vocal cords were in a cadaveric position; there was much deformity of the trachea, but the wall was fixed and the sutures taken through the perforation were still evidently present in the mucous membrane.

June 12, tracheoscopy was done, under ether anesthesia. The trachea was definitely deformed. The cords were about the same. Following an attempt to produce a pancreatitis on this dog, June 8, the animal died, June 13, of a generalized peritonitis and a bronchopneumonia. The trachea appeared as in Figure 4.

EXPERIMENT 5.—Dog 5 was placed under ether anesthesia, Feb. 11, 1924, and a midline incision made in the neck; the muscles were separated, and the trachea was exposed. Both laryngeal nerves (inferior) were isolated and the nerves were stimulated with varying degrees of faradic current. The findings were the same as in Experiments 2 and 3. Both laryngeal nerves were ligated; the cords were found in the cadaveric position with no individual movement.

March 7, both cords were edematous and thickened and without movement. The animal was observed to have periods of dyspnea, especially when eating and during exertion. There was a definite flattening of the chest from side to side, giving a pigeon-breast effect, and the accessory muscles of respiration were being used.

March 21, the dog died from an overdose of anesthetic. The recurrent laryngeal nerve was found ligated about 3 cm. above the superior aperture of the thorax. There were no other pathologic findings.

EXPERIMENT 6.—Dog 6 was placed under ether anesthesia, Feb. 15, 1924, and a midline incision was made in the neck; the muscles were separated, and the trachea was exposed. Both inferior laryngeal nerves were isolated and stimulated with varying degrees of faradic current, while the movements of the vocal cords were examined with the urethroscope. The same results were obtained as in Experiment 3. Seven cartilaginous rings were removed almost completely, subperichondrially. There was definite collapse of the underlying mucous membrane laterally during inspiration. At no time was there any interference with respiration, nor was there dyspnea. The wound was closed in layers.

March 7, a tracheoscopy was done, under ether anesthesia. There was definite stenosis of the trachea in the region of the previous operation, but inspiratory collapse was very much less. The anesthetic was well taken, and there was no dyspnea.

March 21, a tracheoscopy was done, under ether anesthesia. Stenosis of the trachea was definite, the lumen being narrowed by at least one third of its diameter. The collapse during inspiration had entirely disappeared. The anesthetic was well taken.

April 22, the stenosis did not appear as marked as before. The animal was comfortable at all times.

May 9, the dog was placed under ether anesthesia, and the old midline incision was reopened and the trachea carefully exposed. In the region of the previous operation, there was definite scar tissue formation, the tracheal wall appeared firm and did not move during inspiration. The recurrent laryngeal nerves were isolated and stimulated with varying degrees of the faradic current, under deep and light anesthesia, without producing any dyspnea or interference with respiration. An attempt was made to stimulate only the mesial fibers of the nerve, with the dog under very light anesthesia, but abduction of the cords was not produced. Six more tracheal rings were removed almost completely with the result that a progressive inspiratory stridor was produced. Respiration was definitely interfered with and complete collapse of the trachea occurred during inspiration. Two sutures were taken through the tracheal mucous membrane on either side, in an attempt to anchor it to the ribbon muscles, but no relief was obtained. The insertion of a stiff whalebone catheter through the larynx gave immediate relief. The stridor completely disappeared when inspiration became normal. A few hours after recovery from anesthesia, the dog coughed up the tube and died from asphyxia.

A necropsy was performed which was practically negative except for the tracheal condition.

EXPERIMENT 7.—Dog 7 was placed under ether anesthesia, March 10, 1924, and a midline incision was made in the neck; the muscles were separated, and the trachea was exposed. Both inferior laryngeal nerves were isolated, stimulated separately and together with varying degrees of faradic current, under deep and light anesthesia; the result was the same as in Experiment 3. Nine tracheal rings were excised almost completely subperichondrially, with definite inspiratory narrowing of the trachea and slight stridor, but no marked dyspnea or interference with respiration. The wound was closed in layers.

March 21, the dog was comfortable and not dyspneic. Tracheoscopy was done, under ether anesthesia. The cords appeared normal. The trachea wall was irreg-

ularly collapsed and uneven, but there was no visible waving of the tracheal mucous membrane. The animal took the anesthetic well.

April 11, under ether anesthesia, the old incision was reopened, and the trachea was carefully isolated. The wall was definitely covered with scar tissue, and was without movement. The recurrent laryngeal nerves were isolated and stimulated with varying degrees of the faradic current, under light and deep anesthesia, separately and together, but at no time was there any interference with respiration. The left nerve was purposely dissected up to its entrance into the larynx. The cord assumed the cadaveric position, and stimulation of the nerve fibers

Fig. 5.—Specimens in Experiment 8.

was without effect. The right nerve was cut mesially with the result that the cord assumed the cadaveric position; at no time was there any dyspnea. Closure was made in layers.

April 22, a tracheoscopy was done, under ether anesthesia. There was no movement in the left cord. The right cord did not appear to move normally, but was sucked in on inspiration and on expiration returned to its former cadaveric position. The trachea did not appear to be badly deformed. The anesthetic was well taken.

June 12, a tracheoscopy was done, under ether anesthesia. The result was practically the same as that noted, April 22.

EXPERIMENT 8.—Dog 8 was placed under ether anesthesia, March 7, 1924, and a midline incision made in the neck; the muscles were separated, and the trachea was exposed. The recurrent laryngeal nerves were isolated and stimulated, with typical findings. Seven consecutive rings below the cricoid were removed from the left side of the trachea, with slight inspiratory collapse. Stimulation of the recurrent laryngeal nerves was done again, with varying degrees of the faradic current, and, as the animal gradually recovered consciousness, no dyspnea or respiratory difficulty was produced.

March 14, an examination of the trachea disclosed collapse in the region of the left side in front of the trachea, causing distortion of its lumen. There

Fig. 6.—Specimens in Experiment 9.

was a normal outline to the right and behind. The vocal cord movements were normal.

March 21, the results of an examination were the same as on March 14.

April 22, a tracheoscopic examination showed much less collapse and deformity of the trachea.

May 30, following an attempt to produce a pancreatitis, the animal succumbed to a general peritonitis with pneumonia. The larynx and trachea are shown in Figure 5.

EXPERIMENT 9.—Dog 9 was placed under ether anesthesia, March 14, 1924, and a midline incision made in the neck; the muscles were separated, and the

trachea was exposed. Both laryngeal nerves (inferior) were isolated, and the nerves were stimulated with varying degrees of faradic current. The interior of the larynx was examined at the same time with the urethroscope. The result was the same as in Experiment 2. Both nerves were tied lightly with catgut without producing any spasm of the vocal cords, and stimulation above and below the point of ligature was effective. Tugging on the nerves and on the trachea produced no respiratory embarrassment. The nerves were ligated with catgut, with the result that both cords were abducted in the cadaveric position.

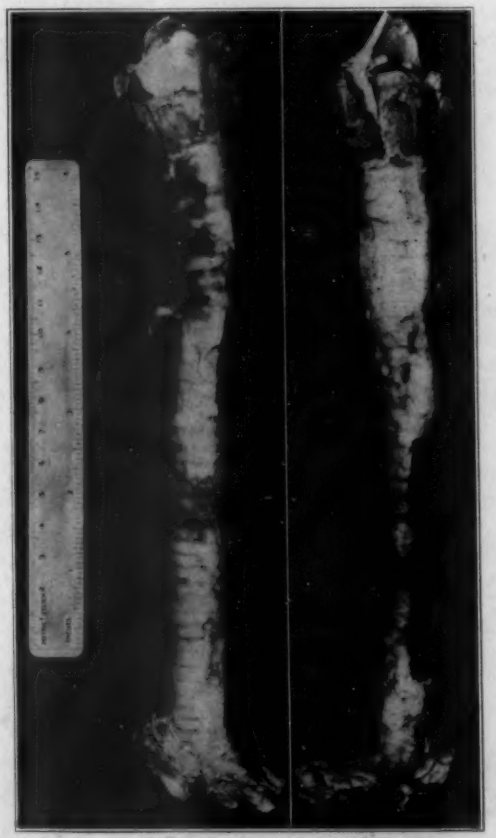

Fig. 7.—Specimens in Experiment 10.

March 21, the cords were in the cadaveric position, and were sucked in with each inspiration.

April 4, a median incision was made. The recurrent laryngeal nerves were isolated and retracted laterally. The trachea was isolated, and nine cartilaginous rings were removed in a zigzag fashion. There was marked inspiratory collapse of the mucous membrane with slight inspiratory stridor, but at no time was there urgent dyspnea or threatening asphyxia.

April 22, under ether anesthesia the cords were abducted, fixed and sucked in with each inspiration. The trachea showed a very marked irregularity of its lumen, the collapse being chiefly in its anterior wall.

June 1, following an attempt to produce an artificial pancreatitis for experimental work, the animal died, the cause of death being a generalized fibrinous peritonitis with a bilateral bronchopneumonia.

EXPERIMENT 10.—Dog 10 was placed under ether anesthesia, March 17, 1924, and a midline incision made in the neck; the muscles were separated, and the trachea was exposed. Both inferior laryngeal nerves were stimulated with varying degrees of the faradic current, under deep and light anesthesia, the results being similar to those obtained in Experiment 1. All tracheal rings were cut in the midline, and the trachea was forcibly collapsed from side to side. There was definite dyspnea, and the accessory muscles of respiration were immediately called into action. Stimulation of the recurrent laryngeal nerves, as was done previously, in no way aggravated the present condition. The two nerves were tied together loosely over the anterior surface of the trachea, being put slightly on a stretch.

March 21, a tracheoscopy was done, under ether anesthesia. The trachea appeared narrowed from before backward, rather than from side to side. The right cord was in the cadaveric position, whereas the left appeared to be more abducted. Both cords showed respiratory movements, the left seeming to move more than the right. The anesthetic was well taken.

April 22, a tracheoscopy was done, under ether anesthesia. Both cords were fixed in a cadaveric position. There was slight passive adduction during inspiration. The trachea was not noticeably narrowed.

June 10, a tracheoscopy was done under ether anesthesia. The cords were in the cadaveric position. The trachea did not appear narrowed. The animal had lost considerable weight, and had been dyspneic since March 21; this dyspnea was increased on exertion. The bark appeared to be lost. This condition, however, had remained stationary since its onset.

November 7, the dog was killed with chloroform. There was practically no deformity of the trachea, as may be seen from Figure 7.

OSTEOPLASTIC SKELETAL METASTASES FROM CARCINOMA OF THE BREAST

REPORT OF AN UNUSUAL CASE

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Metastatic invasion of the skeleton in carcinoma of the breast is of very frequent occurrence. Although many pathologists place its incidence at an average of 20 per cent., some have found its prevalence to be much higher. In Kaufman's series it yielded 53.3 per cent. In Snow's small unselected number of cases, it gave 75 per cent. Observations at the Montefiore Hospital coincide with those of the latter two investigators. During the years 1913-1923, there were admitted to the cancer division of Montefiore Hospital sixty-seven patients with advanced cases of breast carcinoma. Of this number, fifty (74.6 per cent.) showed multiple metastatic lesions in the skeleton, demonstrated either at necropsy or on roentgenologic examination.

This extremely high incidence of skeletal metastases in carcinoma of the breast makes it one of the most important problems, not only to the pathologist and cancer worker but also to the clinician, roentgenologist and radiotherapeutist as well, for breast cancer is one of the deadly triumvirate whose members have been decimating their victims yearly in tens if not in hundreds of thousands throughout the entire civilized world. The mortality from breast cancer is still on the increase. However, the morbidity is much greater than the mortality, and many of the victims of cancer of the breast suffer from symptoms of skeletal metastases for months and years before they finally succumb to this disease.

Moreover, in addition to its extent of distribution and its frequency, skeletal metastasis of breast carcinoma demands the most profound study and the most urgent consideration from the profession because of its peculiar course and clinical symptomatology. Frequently, metastatic invasion of the skeleton is accompanied by the most excruciating pain. At times, it is complicated by spontaneous fracture of the lower extremities. Quite frequently, it invades the vertebral column, giving rise to severe pain and disability long before the general condition of the patient has become markedly impaired. The magnitude of this clinical problem can best be appreciated by those who have seen patients with metastatic carcinoma of the spine or lower extremities bedridden for months and sometimes years, with all their mental faculties fully intact and the general condition fairly well preserved, but painful burdens to themselves and to their attendants.

The following case of osteoplastic skeletal metastases from a carcinoma of the breast presents such a great variety of highly interesting and instructive clinical data that the rather lengthly presentation is deemed fully justified.

REPORT OF CASE

History.—The patient was a married woman, aged 57, whose family history was negative. There was nothing in the personal or menstrual history that had a bearing on the present condition. She had been married twenty-eight years, had given birth to three children, nursed each one a year, and had had no mastitis. In 1897, she suffered from acute articular rheumatism for several months. In 1903 and in 1913, she had acute attacks of biliary colic with jaundice, fever and enlarged liver and gallbladder; each attack lasted from two to three weeks. Recovery occurred under expectant treatment.

In 1904, she accidentally discovered the presence of a painless lump, the size of a small walnut, in her right breast. Immediately she consulted a physician, who assured her of the benign and harmless character of the growth. Two months later, failing to note any recession or diminution in the size of the mass, she consulted another physician, who likewise assured her of the benign character of the lesion, and told her to forget about it.

As it gave her no pain or discomfort she was ready to follow the doctor's suggestion. Shortly after the consultation, she accidentally struck her right breast, and the lump immediately became painful. When, a week or two later, she again sought medical advice for the now painful lump, she was referred to a surgeon, who advised immediate operation. A right mastectomy was performed shortly afterwards. The preoperative and postoperative diagnosis was a malignant growth of the right breast. The postoperative course was uneventful, except that the wound was rather slow in healing and left large keloidal scars.

The present illness dates back to the early part of 1916, when the patient began to suffer from bilateral dental neuralgia and frequent recurring occipital headaches. In July, 1916, she noticed the presence of a hard lump in the occipital region. This lump was neither painful nor tender. Only occasionally in moist weather did she experience an uncomfortable sensation over it which barely amounted to a distinct pain. For three years, the lump remained practically stationary, and towards the close of 1920 it apparently began to decrease in size. About July, 1920, a second lump appeared over the parietal region. This lump did not remain stationary in size, but underwent periodic increase and decrease, with a tendency to progressive growth. In December, 1920, a third lump appeared over the frontal region.

About the middle of 1919, she began to suffer from frequent generalized headaches, which lasted from twenty-four to forty-eight hours. These would be preceded by a day or two of nausea and a tightening sensation over the scalp, which later changed into a distinct feeling of formication. On the second day following the appearance of the headache, swelling of the scalp would develop, which, after lasting two or three days, would gradually subside. In October, 1920, she would occasionally also have a gummy discharge from the pharynx accompanying the headaches.

When she consulted me the first time concerning this condition, Dec. 18, 1920, the physical examination showed the following: The patient was an elderly woman, well nourished and developed; she showed no pallor, cyanosis

or edema; her mentality and affective sphere were normal. Examination of her eyes, teeth, throat, tonsils and thyroid was negative; the chest, lungs and heart presented nothing abnormal; the pulse, temperature and respiration were normal. The blood pressure was 155 systolic, 90 diastolic. Nothing abnormal was found on abdominal or vaginal examination; examination of the extremities was negative, and the knee jerks were normal.

The only positive findings were in: (1) The skull, where three bony, hard masses, from 2 to 1 inch in diameter, were felt, the largest situated in the occipital region, and the smallest in the parietal and frontal regions. The tumors were neither tender nor painful. There was a slight edema of the forehead extending to the upper eyelids. (2) The right breast, which showed a healed mastectomy scar with marked keloidal overgrowth. There was no induration or nodule formation in the entire area, and the axillary lymph nodes were not palpable. A blood Wassermann test taken at that time was reported negative.

A roentgen-ray examination of the skull showed a diffuse increase of bone formation with a small area of destruction. The roentgenologic diagnosis was positive typical gumma. This roentgen-ray diagnosis was imparted to the husband of the patient, who strenuously denied any syphilitic or other venereal infection. This denial plus the negative Wassermann report precluded for a time the use of antisyphilitic medication, and the patient was placed on salicylates and sedatives to produce temporary relief.

Feb. 28, 1921, the patient again called at my office complaining of recurring edema of the scalp, which had begun February 14 and, after gradually spreading downwards over the forehead, had caused marked swelling and closure of the left eyelid. The edema had cleared up within five days, but the rheumatic pains over the lumps were quite annoying. On physical examination, no new findings were discovered. The urine and blood examination failed to show anything abnormal. Thinking of the possibility of focal infection from diseased sinuses, I had her examined by one of our foremost nose and throat specialists. The examination failed to reveal anything pathologic, in spite of the fact that the gummy discharge which the patient had noticed at the height of attacks of headaches still kept recurring. I asked for an expression of his opinion about the nature of the lumps on the head, but the consultant would venture none. He had never seen a similar case, and did not care to indulge in wild guesses.

The case appeared exceedingly puzzling to me, and I suggested further consultation. This decision was readily accepted, and the first week of March, a prominent New York internist examined her and suggested three possibilities: (1) metastatic hypernephroma; (2) myeloma; (3) inflammatory lesion of bone. After making this tentative diagnosis, he frankly confessed that he had never before seen a similar case, and he advised me to consult a well known orthopedist.

This advice was soon followed. In April, at the time of the consultation with the orthopedist, her chief complaints were (1) "rheumatic" pains in the lumps of the head, (2) edema and soreness of the scalp, and (3) fluctuation in the size of the lumps.

After a thorough study, the case appeared very puzzling to this new consultant. He would venture no diagnosis, but suggested atophan treatment for ten days. When, at the end of that time no improvement occurred, he advised consultation with a New York internist whose experience with bone tumors he considered unique and most extensive.

April 10, this consultation took place. At that time, the patient stated that during the last three days a fresh lump had appeared over the right temple.

This was accompanied by mild pain over the skull and a moderate febrile reaction to 101 F. After a most exhaustive examination, her condition appeared just as puzzling to this consultant as it had to his former colleagues. He considered four possibilities: (1) Syphilis; (2) neoplasm; (3) inflammatory lesion, or (4) endocrine disturbance. Of these four possible diagnoses he favored the first, mainly because of the presence of bone tenderness over the left parietal region, which failed to show any accompanying enlargement of bone. In this opinion, he was soon strenghtened by an admission of the patient's husband that he did have a syphilitic infection one year before his marriage.

Treatment.—A positive diagnosis of syphilitic bone disease having been made, antisyphilitic treatment was recommended to be pushed very vigorously, in spite of two or more negative blood Wassermann reactions obtained immediately after this consultation. For one month, very energetic treatment with mercury, arsphenamin and iodids was carried out without, however, producing any influence on the patient's symptoms or signs.

Course.—With the failure in treatment came a demand for further consultation. In May, she was seen in consultation with a prominent cancer specialist, who, after a thorough clinical examination and a study of the skull plates, had another new series of roentgen-ray plates taken of her skull. The roentgenologic study of all the plates revealed a proliferative ossifying periostitis. A diagnosis of syphilitic bone disease was made, and a vigorous continuation of the antisyphilitic treatment was urged.

In June, another roentgen-ray plate of the patient's skull was taken, and comparison with former plates elicited the opinion of the same consultant, "More new bone production; condition apparently improved."

Symptomatically, however, the patient was not improving. New lumps kept appearing, accompanied by pain, tenderness, redness, edema and slight fever at the height of each attack. July 20, while she was still receiving very active antisyphilitic treatment, the following note was made: For the last three days the patient had been complaining of numbness of her right lip, severe radiating pain along the left side of her neck and shoulder regions, occasionally reflected as far down as her finger tips. A roentgen-ray examination of her cervical spine and skull, made at that time, failed to show any pathologic lesion in the cervical vertebrae. The skull, however, showed more extensive changes than it had on prior examination. The roentgenologic diagnosis again was syphilitic bone disease.

The patient became importunate in her demand to have prompter relief than she saw forthcoming, and, to shed more light on this apparently obscure and obdurate condition, a joint consultation was held in July with three of the most prominent New York physicians, two internists and one neurologist. After a thorough study of the clinical and roentgenologic data plus an ophthalmoscopic examination of the eye grounds, a great deal of deliberation followed, but no agreement in diagnosis could be reached. Each one of the three consultants expressed a different opinion. One diagnosed Paget's disease, another osteoperiostitis of unknown origin; the third strongly favored a syphilitic bone disease, especially because of the presence of the optic neuritis. They were all unanimous in their opinion that the eye grounds ought immediately to receive further study by an expert ophthalmologist before any course of treatment was decided on. To make the findings doubly sure, two of the most expert and prominent ophthalmologists in New York were consulted. Both men reported: bilateral choked disk, concentric contraction of the visual fields, endarteritis

obliterans and capillary retinal hemorrhages. The etiology was unknown; it was either syphilis or neoplasm.

In the meanwhile, the patient's symptoms took a sharp turn for the worse. Her headaches became excruciating. She complained of considerable blurring of vision. When the ophthalmologist's report was received, the neurologic consultant and one of the internists were strongly in favor of a decompression operation on the skull; for the danger of sudden blindness appeared to be imminent, and not to be prevented except by surgical means.

Fig. 1.—Carcinoma of the skull, July 12, 1921. Diffuse osteoplasia with areas of bone absorption.

The patient, however, refused to submit to an immediate decompression operation, and insisted upon further consultation before consenting to any operative intervention. The new consultant, a man of wide experience with bone tumors, suggested in turn another ophthalmologic and neurologic consultation. This consultation was held in the early part of August. The opinion of both consultants was that the patient had syphilis; vigorous antisyphilitic treatment and careful watching for any further eye symptoms before the patient was submitted to a decompression operation were recommended.

On August 12, she complained of pain in the right jaw, of numbness of the right upper lip and pain in the left upper extremity. A lumbar puncture done on

this date showed clear fluid, under normal pressure. The Wassermann reaction was negative, and no other abnormal findings were discovered. Nevertheless, the three new consultants urged further vigorous administration of antisyphilitic therapy. For three months this treatment was continued, and arsphenamin and mercurial injections were pushed to full tolerance. However, there seemed to be no definite improvement, and towards the end of October the treatment was temporarily discontinued.

November 1, the patient began to complain of severe aching pain in her left axillary region, and on examination slight thickening and moderate tenderness were elicited over the left eighth rib. In addition, the pain in the skull, in the cervical region, radiating down both upper extremities, kept recurring periodically in undiminished form. At this juncture, at a loss to allay the severe suffering of the patient by ordinary sedatives and extremely unwilling to resort to morphin, I suggested the use of "radium pack" mainly for its analgesic effect, for at that time the possibility that this patient was suffering from multiple skeletal metastases of a breast carcinoma removed seventeen years before had not been suspected by any of us.

The suggestion to use radium met with approval, and for the next four months, until March, 1922, she was under the care of a prominent radiotherapeutist who administered external applications of radium to her skull from one to three times weekly. The result of this new form of therapy plus a continuation of the antisyphilitic treatment was apparently productive of an improvement in her general condition, and moderate relief from pain was secured. Concomitant with this general and local improvement, repeated examinations of the eye grounds showed gradual and progressive improvement.

About the middle of March, 1922, her severe frontotemporal headaches recurred. However, an ophthalmoscopic examination at this time revealed normal eye grounds.

The patient's condition now appeared hopeful not only to herself but also to her medical attendants. All concerned began to feel that the persistent antisyphilitic treatment had certainly produced favorable results, and that the use of radium was a definite benefit. One week later, when hopes ran highest, the patient suddenly developed recurring severe headaches. Her left eyelid began to swell, and within twenty-four hours was completely closed. On physical examination, the left temporal region was found to be very painful and tender and the left occipital region moderately so. A roentgen-ray examination of the skull made at that time showed no change in the bone lesions. The patient grew despondent. The family insisted upon further consultation. A biopsy had been suggested several times previously but was persistently refused. It was now again recommended and finally accepted conditionally upon consent and approval by and after consultation with a celebrated out-of-town bone tumor specialist.

Towards the end of March, this consultation was held. After a complete and thorough study of all the clinical, laboratory and roentgenologic data in this case, a careful restudy and cross-examination of the patient's symptomatology and clinical course was begun by this consultant. In addition, he had a new series of roentgenograms taken of almost her entire skeleton. The urine was examined for Bence-Jones bodies. An expert otolaryngologic examination was also obtained and pronounced negative.

The diagnosis made after this most complete and exhaustive study was ossifying periostitis, Garre type. The etiology was a focal infection, probably dental in origin. He would consider neither syphilis nor neoplasm. He saw

no reason or indication for doing a biopsy, and advised removal of the remaining teeth, eight in number, even in the presence of negative roentgen-ray findings. Based upon this diagnosis he gave a favorable prognosis.

The patient was informed of the favorable outlook of her case, but was cautioned of the possibility of a prolonged fight until the focus or foci of local infection should be definitely found out and eradicated. She was greatly impressed by the personality and opinions of this celebrated consultant. Her spirits rose, and depression was gone. Even her physical pain seemed tem-

Fig. 2.—Carcinoma of the skull, May 2, 1922. Extensive osteosclerosis, with areas of rarefaction.

porarily to have completely disappeared. This did not last long. During the journey to New York, the headache returned with increased severity, and her left eyelid began to swell. When she reached New York, the eye was completely closed. In rapid succession there was recurrence of pain in the posterior cervical region, drawing pain in the condemned teeth, and moderate soreness over the eighth and ninth ribs in the left midaxillary region. In addition, a new, tender erythematous nodule had made its appearance over the left side of the forehead, which, after persisting for ten days, gradually disappeared. The neuritic pain down the left upper extremity became quite

severe. A new site of invasion was evidenced by swelling of the left upper jaw extending to the submaxillary and submental regions.

The remaining teeth were considered as a cause of these painful areas, and were extracted. Around some of the roots a mild pyorrheal condition was found, but no extensive infection was discovered.

Eight weeks later, on July 5, the following note was made: During the last eight weeks the patient had felt fairly comfortable; she had been free from headaches during all that time; only occasionally did she experience slight pain in the posterior cervical region, radiating down the left upper extremity to the finger tips. However, mild swelling of the scalp kept recurring as of old, and once or twice her left submaxillary region became swollen. Her general condition, nevertheless, was excellent. She looked well, ate and slept well, and was in no need of sedatives.

In spite of this subjective improvement physical examination revealed definite rigidity of the neck, and the cervical spine was tender and painful. Motion was limited and was accompanied by an increase in pain. The rest of the examination was negative, with the exception of the persistence of nontender nodes over the skull.

In the early part of August, she went through an attack of acute cholecystitis, accompanied by fever, jaundice and an enlarged gallbladder. During this attack, all her skeletal symptoms were entirely in abeyance. During the latter part of the same month, she was reexamined by the same out-of-town consultant, who reaffirmed his diagnosis of infectious ossifying periostitis, and advised mixed vaccine treatment.

A few days after this favorable opinion was expressed a rapid recurrence of severe pain from multiple bone lesions in the skull, cervical spine, jaws, upper extremities and ribs made the patient's condition a sorry plight indeed. Sedatives had to be used liberally, but were productive of very little relief.

Her condition looked grave, and the prognosis began to look quite ominous to me. After watching the clinical course and symptomatology of this puzzling case and pondering over the various diagnostic possibilities, I became more and more convinced that this patient was suffering from a progressive invasion of her skeleton, which was slowly and steadily making further inroads in spite of all the therapeutic measures that were being used in her case. Moreover, having become familiar during that year with the clinical course and behavior of skeletal metastases of carcinoma in general and breast carcinoma in particular, I was gradually forced to accept the conviction that this patient was suffering from a late development of skeletal carcinosis from the breast carcinoma that was removed eighteen years before.

I expressed this opinion to her husband, and urged a biopsy of her skull, to settle once for all the diagnosis and nature of this baffling and extremely painful case. This suggestion was accepted, but so great was the faith of the patient in the out-of-town consultant that she would have no other surgeon perform the biopsy.

Diagnosis.—She left New York October 7, and had a biopsy of her skull performed the same week. The pathologic report came back adenocarcinoma. This diagnosis was confirmed by two eminent pathologists. This revelation was so unexpected and astounding that it clearly dumbfounded the consultant. The outlook was that of a speedy, hopeless, downward course. This pessimistic view was greatly favored by the severe pain the patient was now suffering, and by the rapid increase in morphin medication made necessary by the aggravation in the agonizing pain shortly after the biopsy. The patient rapidly deterio-

rated in health and strength. She soon became bedridden and her entire morale became undermined. Her condition looked so hopeless that death seemed imminent.

As soon as a definite diagnosis of skeletal metastasis of breast carcinoma was made, I began to urge in my correspondence with the patient and the consultant the use of high voltage roentgen-ray therapy as an analgesic and palliative measure. At first this suggestion met with very little approval, for the patient's condition was considered extremely unfavorable. Moreover, Dr.

Fig. 3.—Photomicrograph of section removed from tumor of skull, showing adenocarcinoma (courtesy of Dr. J. C. Bloodgood).

C., the consultant in charge, expressed his utter lack of faith in the therapeutic efficiency of radiotherapy in skeletal metastases. Accordingly, the patient was being fed larger doses of morphin and smaller rations of diet as her strength and digestive capacity decreased and her pain increased.

In January, 1923, after three months of a progressive, downward, bedridden course, the family finally decided to bring the patient back to New York. When I saw her on January 10, the day after her return to New York, she presented a most pitiable sight. Within the space of three months, she had aged greatly. She looked wan and wasted, and her eyes were bleary and bulging. Her facies presented the depressed and befuddled look of the confirmed morphin habitué.

However, after the most careful physical examination, the skeletal metastases apparently showed no progression. There was no clinical evidence of malignancy in any of her viscera. Again I urged the cautious but persistent use of roentgen-ray therapy in her case. So thoroughly, however, were the patient and the family impressed with the views of the out-of-town consultant in regard to the uselessness of radiotherapy in her case, that it was not until Dr. James Ewing of New York was called in consultation and urged the persistent use of high voltage roentgen-ray therapy in her case, that final consent was obtained for this mode of treatment.

Finally, on January 30, the patient was admitted to the Van Courtlandt Hospital, ready to undergo irradiation treatment. On admission, her chief complaints were: (1) profound weakness (bedridden state); (2) severe lancinating pain in the head, neck and shoulders, requiring the regular administration of morphin, one-half grain (0.032 gm.) from every four to six hours; (3) marked depression and irritability. On physical examination, the patient was found moderately pale and slightly cachectic-looking, dulled when under the influence of morphin, violently irritable when the pain returned and the craving for the drug became urgent. She presented no dyspnea, cyanosis or edema. In the upper occipital region of the skull, in the vicinity of the biopsy scar, there were present eight, hard, bony, nontender nodules each about 2 cm. in size, and about 3 to 4 mm. above the level of the scalp. A few of the nodules were denuded of hair and presented a bluish discoloration and dilatation of venules. Numerous smaller discrete nodules were scattered over the rest of the skull. The large occipital node that had made its first appearance five and a half years before had undergone considerable reduction in size. All the cervical and upper second and third dorsal vertebrae were moderately tender. The cervical spine was moderately rigid, causing pain and moderate limitation of motion. Both upper maxillae presented enlargement and thickening, more marked over the left than the right. There was no tenderness or edema. The pupils were contracted, and responded very sluggishly to light and accommodation. Sight and hearing were apparently normal. Examination of the throat, heart, lungs and abdomen was negative. The blood examination showed: red blood cells, 3,100,000; hemoglobin, 55 per cent.; white blood cells, 11,000; polymorphonuclears, 64 per cent.; small lymphocytes, 22 per cent.; large lymphocytes, 10.75 per cent.; mononuclears, 3 per cent.; eosinophils, 1 per cent. The urine examination revealed: albumin, a heavy trace; no glucose; white blood cells, a few.

Roentgen-ray examination of the right shoulder revealed moderate arthritic changes. There were moderate arthritic changes in the left shoulder and bone absorption involving the lower half of the glenoid of the scapula and a small area of absorption in the head of the left humerus. Examination of the chest and lungs, the pelvic bones and the upper femora was negative.

Systematic treatment with high-voltage roentgen rays was started February 2, and repeated at definite intervals according to clinical and radiographic indications. The technic used was: voltage, 200,000; target distance, 50 cm.; filtration, copper, 0.5 mm.; aluminum, 1 mm.; milliamperage, 4; portal, 15 by 15 cm.; time, 90 minutes (skin erythema dose). This dose was to be repeated over each field in four to six weeks. If half a dose was administered, forty-five minutes was taken, and it was to be repeated in four to five days.

Clinical Course After Irradiation Treatment.—February 8, the patient felt improved. She rested comfortably through the night and sleep was sound. She experienced no nausea or vomiting after the treatment. The pain in the cervical and the shoulder regions had diminished considerably. The edema of

the left eyelid was clearing up, and there was less pain in the lower spine on motion. Appetite and strength were improving.

February 15, the patient was able to leave her bed for the first time after a bedridden state of more than three months. The dose of morphin had been reduced to one-half that given for months before radiation was started. This improvement continued and, six weeks after her admission to the Van Courtlandt Hospital, the patient was discharged greatly improved in her general health; the dose of morphin was reduced to one-eighth grain (0.008 gm.) two to three times daily.

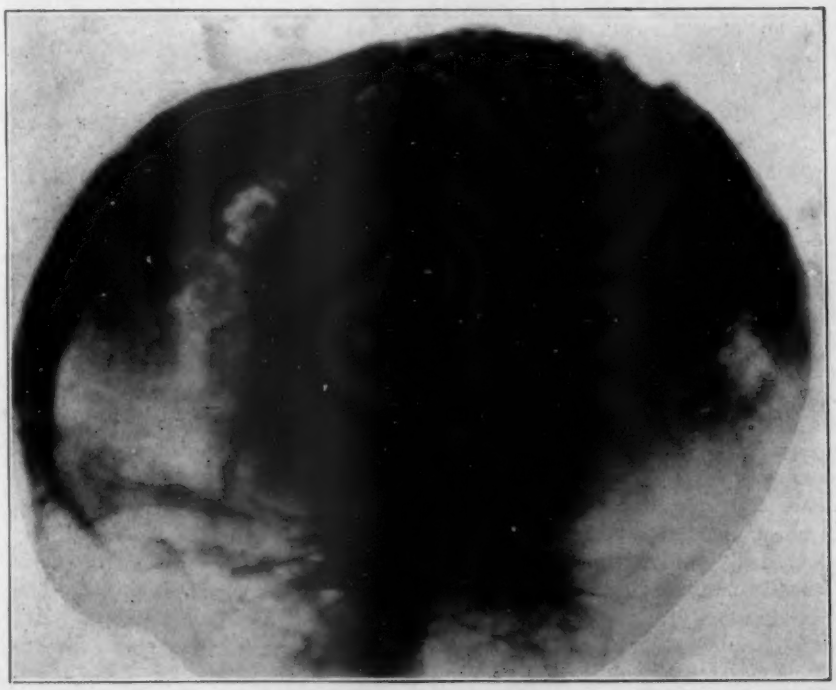

Fig. 4.—Carcinoma of the skull, Jan. 3, 1924, one year after high voltage roentgen-ray treatment. Very marked, diffuse new bone formation, with some areas of bone destruction.

Following her discharge from the hospital, the high-voltage roentgen-ray treatment was continued at regular intervals according to clinical indications.

Towards the end of April, not only was there general symptomatic improvement, but the nodules over the skull were distinctly diminished in size. On June 1, the following note was made: The chief complaints were depression, generalized aches and pains. The violent agonizing pains which the patient used to suffer before the commencement of high-voltage roentgen-ray therapy had not recurred. She had gained moderately in weight and in strength. An examination of the entire skeleton failed to reveal any area of tenderness. Examination of the chest, lungs and abdomen was negative. The only positive findings were a moderate rigidity of her neck and a bloated appearance of her

face, which we attributed more to the morphin administration than to the skeletal metastases. For, in spite of the undoubted diminution in the severity and frequency of the pain from the cancerous invasion of her skeleton, the patient had become a confirmed morphin addict, and one-eighth grain (0.008 gm.) of the drug had to be administered by hypodermic injection a few times daily, or withdrawal phenomena would immediately supervene.

By the middle of June, the radiation treatment was temporarily discontinued, and the patient was advised to go to the country for several weeks to build up her general health. She left for the Catskill Mountains June 14, and returned about the middle of July. During her stay there her appetite and bowels were in exellent condition, and she was not bedridden. She was out of doors all day, took an interest in her surroundings, and was very sociable and interested in company. She conversed a great deal, and only rarely referred to her illness as a topic of conversation. She had apparently become a morphin habitué, for she was cheerful, gay and hopeful when under its effects and depressed when the craving for the drug returned. During the last week of her stay in the country, a recurrence of pain in the lower cervical and upper dorsal spine and in the left shoulder region had taken place. However, her general condition remained fair. She had lost no weight, and walked with a fairly firm gait. There was no pain in the spine on walking or stooping forward, and there was perfect freedom and painlessness on motion of all the joints with the exception of the cervical spine. The nodules over the skull had almost entirely receded. Alopecia of the scalp was almost complete.

The impression obtained after a thorough study of present symptoms and signs was that she would have been in an even more comfortable condition if she could have been freed of her morphin habit. A strenuous effort was now made to reduce the dose of the drug gradually. In this attempt, only partial success was obtained, because of lack of cooperation on the part of the nurse. However, in September and October the dose was gradually reduced to about one-sixteenth grain (0.004 gm.) two to three times daily.

About the middle of September, she began to have a dull ache in the sacrococcygeal region, radiating at times down the posterior aspect of her right lower extremity to the toes. Occasionally, her cervical spine ached, and she felt a choking sensation in the pharynx. At rare intervals, a drawing pain was felt in the right shoulder, and a dull ache in the frontal region. A roentgenologic examination made at this time revealed less bone destruction and more new bone formation in the skull. There were, however, definite areas of bone destruction in her fifth and sixth cervical vertebrae. The left glenoid of the scapula showed no progression of the bone destruction noted on the former plates. Examinations of the ribs, lungs and the mediastinum were negative.

October 1, when her general condition seemed most excellent, she suddenly began to have severe pain in her sacral region, radiating down both lower extremities. Stooping forward became limited and painful, and she walked with a limp. After two treatments of forty-five minutes each over the sacrum, administered at intervals of four days, the sacral pain gradually subsided and the limp disappeared. However, the cervical spine began to show signs of increased metastatic activity. She experienced a choking feeling in her throat, as though the bones of the neck were growing together with the flesh and skin, which caused a sensation of dragging down of the chin towards the chest wall. In addition, there were radiating pains from the spine along the entire body. Two weeks later she developed severe pain in the left shoulder followed

by disability and stiffness. At about the same time, the right lower jaw commenced to swell, and for a few days she ran a moderate febrile course.

Following another course of high-voltage roentgen-ray therapy, there was again gradual relief from pain, swelling and disability. About the middle of November, the pain in the cervical spine had almost entirely subsided, and the rigidity became less. There was only slight limitation of motion on abduction in her left shoulder, while all the other motions of the joints were free and painless. The nodules in the skull, which had begun to grow again in October, had again yielded to roentgen-ray therapy, and had diminished to one-half their former size. The pain and tenderness along the entire spine had completely disappeared, and the patient could stoop forward and touch her toes without any discomfort. The physical examination of the chest, lungs and abdomen was negative. There was an improvement in the general condition, and she gave the appearance of having gained in weight and strength.

November 19, the patient was readmitted to the Van Courtlandt Hospital for one week. This was done more with the object of ridding her, if possible, of the morphin habit, than for the sake of receiving a new course of roentgen-ray treatment. For a few weeks prior to admission to the hospital, the severity of the pain from the skeletal metastases had been gradually diminishing, and it was now considered opportune time to try the complete withdrawal of the use of morphin. In this attempt, we fully succeeded during the first three days of her stay at the hospital. The initial dose given by hypodermic injection the first night was $\frac{1}{32}$ grain (0.002 gm.) morphin. This was reduced the second night to $\frac{1}{64}$ grain (0.001 gm.) and on the third to $\frac{1}{128}$ grain (0.005 gm.). On the fourth night, only a hypodermic injection of sterile water was given and this was kept up for about two weeks, when the patient herself asked to discontinue its use. She was discharged from the hospital November 26, and after that date received no morphin. Mild doses of codein were allowed, from one-eighth to one-fourth grain (0.008 to 0.016 gm.) twice or three times daily.

The first week in January, 1924, the patient was reexamined and found to be greatly improved in her general condition. The members of her family were so impressed by her seemingly healthy appearance that they all began to doubt the correctness of the diagnosis.

About the middle of January, however, she began to have a dull, aching pain in the sacral region. A complete roentgenologic study was made. The roentgenologic examination failed to reveal any gross pathologic changes in the lumbar spine or in the pelvic bones. Examinations of the chest and lungs were negative. The cervical spine showed no progressive destructive change. The skull disclosed an increase of new bone formation. The pain over the lumbosacral region increased in severity.

February 14, she was readmitted to the Van Courtlandt Hospital for a series of high-voltage roentgen-ray treatments applied to the sacrolumbar region. An examination of her blood made on admission showed: hemoglobin, 85 per cent.; red blood cells, 4,100,000; white blood cells, 5,000; lymphocytes, 38 per cent.; polymorphonuclears, 58 per cent.; mononuclears, 4 per cent.

The general condition of the patient was fair, and her appetite continued good. February 25, after the fourth roentgen-ray treatment, she was able to sit up in bed without pain. February 29, she was able to leave her bed and walk about the room. March 13, she left the hospital with the pain and disability in her lower spine completely relieved. A reexamination of the blood at time of discharge showed: red blood cells, 4,250,000; hemoglobin, 90 per cent.; white blood cells, 7,000.

COMMENT

Diagnostic Considerations.—In reviewing the history of this case one is struck by the readiness with which all physicians consulted in this case declared in favor of an inflammatory bone lesion and against tumor growth. Moreover, it is remarkable how the majority of the men diagnosed syphilitic bone disease and clung to this opinion tenaciously in spite of the negative response of the blood and the cerebrospinal fluid to the Wassermann test, and the lack of improvement after a prolonged and most intensive course of antisyphilitic treatment. When a suspicion of bone malignancy was expressed by any of the men, it was immediately discarded as an utter improbability. Not one of the numerous consultants who examined this patient suggested even a remote possibility of late skeletal metastases from a carcinoma of the breast removed nineteen years before.

Why was there no suspicion aroused in the minds of any of these physicians, who are among the acknowledged leaders in the profession, of the presence of bone malignancy in this case?

Was it entirely due to the late appearance of the skeletal metastases without any evidence of local recurrence? I hardly think so, for there have been numerous reports in the literature of local and metastatic recurrence of breast carcinoma, ten, twenty or even thirty years after the original mastectomy operation was performed. The physicians who saw this patient in consultation presumably must have been familiar with the late recurrence of breast carcinoma. Why, then was skeletal metastases not even suspected in this case? Was the excessive new bone production, which so closely simulated a benign ossifying periostitis or osteitis, solely or chiefly responsible for this failure to diagnose a malignant bone lesion?

Probably to a certain degree it was responsible, for skeletal metastases in breast carcinoma most frequently gives rise to discrete and destructive, and not to diffuse and osteoplastic, lesions of bone. However, ossifying or osteoplastic skeletal metastases in carcinoma is a familiar condition to every student of cancer pathology. Although the predominant form of bone metastases in carcinoma of the breast is osteoclastic, enough has been written in the literature on the presence of an osteoplastic phase to make it familiar to the profession. According to Kaufman, the osteoplastic type yields at least 14 per cent. of the skeletal metastases in carcinoma of the breast.

If it was neither the lateness of the recurrence nor its type which was solely or chiefly responsible for this failure in diagnosis, what was it that completely barred all suspicion of skeletal carcinomatosis in this case?

It seems to me that the only plausible answer that can be given to this question is: It was primarily the clinical course, which in every

essential feature was so like that of a benign inflammatory condition, completely warding off all suspicion of a carcinomatous bone lesion, that was chiefly responsible for this failure in diagnosis. The merest whisperings of suspicion that this puzzling case possessed an underlying carcinomatous nature would cause the following objections to be raised:

Would skeletal carcinomatosis be likely to arise twelve years after a successful mastectomy operation for a breast tumor, without any evidence of local recurrence? Would a skeletal carcinoma be likely to develop slowly over a period of three and one-half years, and then become quiescent and recede? Would a second carcinomatous nodule be likely to make its appearance three and one-half years after the first, develop and grow for several months, undergo fluctuations in size, and likewise recede? Would carcinomatous nodules keep on appearing and disappearing and be accompanied by severe pain, edema, redness, tenderness, swelling and fever, repeatedly closing either one eyelid or the other and then completely receding? Would multiple carcinomatous bone tumors keep on appearing and disappearing over a period of five years and the patient apparently remain in fair general health, without loss of weight, anemia and cachexia? Would a carcinomatous tumor cause advanced bilateral choked disk, which would completely clear up with complete restoration of visual function? Would not on the contrary a malignant tumor, especially a carcinoma, be apt to show a continuous, progressive growth without those frequent remissions which this patient so strikingly presented?

These and many more objections could have been raised in the past, and would have been raised today were it not for the biopsy done by Dr. Bloodgood and the diagnosis of adenocarcinoma definitely established, microscopically by himself and Dr. James Ewing. So utterly unbelievable does this diagnosis appear even today to many of the physicians who have had the opportunity to study this case that, I believe, Dr. Bloodgood is voicing the sentiments of the majority when, in a personal communication on January 4, 1924, he writes: "Were it not for the microscopic study of the sections from the growth of bone on the skull, I would still feel I was dealing with a benign, multiple disease of the skeleton. . . . It seems remarkable that Mrs. P. is now living almost two years since I first saw her."

With the diagnosis of skeletal carcinomatosis definitely established, the most important question that confronts us now is this: Is this case merely a unique and isolated example, infringing on all the rules of the behavior of skeletal metastases in carcinoma, and therefore only of interest as an anomaly in the medical curiosity shop? Or, on the contrary, is this case only a more striking example of a process and behavior of carcinomatous skeletal metastases, especially in the osteoplastic types?

To these questions, the answer is: Skeletal carcinomatous metastasis giving rise to marked inflammatory reactions, noninfectious in origin, and accompanied by frequent remissions, is not at all a rare phenomenon in the evolution of carcinomatous growth and is frequently met at the bedside and in the clinic of any large cancer service. Its failure to receive adequate recognition in life and literature is due mainly if not entirely to the undervaluation of clinical study and observation in general, and cancer clinical study in particular.

Among pathologic anatomists, the importance of this inflammatory reaction in skeletal carcinomatosis has been recognized for a great many years. In 1886, Lanzinger wrote about it. In 1891, Von Recklinghausen championed the theory that it was this noninfectious inflammatory reaction that was responsible for the new bone formation in osteoplastic skeletal metastases. In this view he was upheld by many pathologists (Askanazy, Asseman, Courvoisier, Fischer-Defoy, Kaufman, etc.). The histopathological literature is replete with numerous cases of osteoplastic skeletal metastases in which the inflammatory reaction was unusually prominent. In a series of cases studied by Kaufman, this inflammatory reaction was so striking that he thought this form of carcinomatous lesion fully deserved the designation, "carcinomatous osteitis."

That this noninfectious inflammatory reaction is a striking feature not only in osteoplastic skeletal metastases but is a frequent accompaniment in the development of malignant neoplasms in general is maintained by Ewing.

In recent years, especially in breast carcinoma, no one has more emphasized this phase of carcinomatous growth and activity than Handley. In his classic monograph on cancer of the breast, Handley formulates his illuminating conception of the life cycle of every carcinoma thus: "Every aggregation of carcinoma cells has a definite life cycle, and after increasing in size for a varying period and at a varying rate, tends spontaneously to undergo degenerative changes. . . . The degenerative changes excite an inflammatory reaction in the surrounding tissues, which ends in fibrosis. . . . These changes extend from the center of the mass centrifugally to its periphery, lead to its shrinkage, and terminate in the replacement of the aggregation of cancer cells by a fibrous scar." According to Handley, it is this noninfectious inflammatory reaction followed by fibrosis that is frequently responsible for the local cure of carcinoma or for its spontaneous recession or remission.

Unfortunately, however, while this noninfectious inflammatory reaction in carcinoma in general and skeletal metastases in particular has received a great deal of study and investigation from numerous pathologic anatomists and histologists, the clinical side has been sorely

neglected. In looking up the references in the Index Medicus on the clinical literature on skeletal metastases for the last twenty-nine years, since Roentgen's discovery of the roentgen rays made this form of carcinomatous lesion readily demonstrable during the life of the patient, hardly more than half a dozen clinical reports were found. Furthermore, in those reports the clinical course of the skeletal metastases was not the main object of the study, but was usually subsidiary to the pathologic or therapeutic phase of the presentation.

After a careful perusal of the clinical literature that has been published on carcinomatous skeletal metastases, one is thoroughly convinced that it was this neglect to observe carefully and to record the clinical manifestations of skeletal metastases which was chiefly if not entirely responsible for the failure to diagnose our case, and for the surprise expressed when the biopsy finally revealed the carcinomatous nature of the bone lesion.

Therapeutic Considerations.—To evaluate properly the use of high-voltage roentgen-ray therapy in our case is rather difficult. The patient suffered from one of those rarer cases of carcinoma in which the natural resistance or immunity is high. This is evidenced by the long duration of her carcinoma, eighteen years before therapy was started. The active manifestations of the skeletal metastases in her case repeatedly showed those spontaneous remissions which, although rare, have been repeatedy observed and recorded in the literature (Rhodenburg).

Furthermore, in spite of quite extensive and intensive high-voltage roentgen-ray therapy, her disease had neither been cured nor arrested. The process, like a slow smouldering fire, had been spreading on and on, and periodically still showed exacerbations in the form of violent outbreaks of pain in various regions of her skeleton. We cannot therefore claim either cure or arrest of the disease.

Have we, therefore, entirely failed in our endeavors to benefit our patient by radiation therapy? Hardly so. When this patient returned to New York in January, 1923, she was rapidly going down hill. She was bedridden, in agony when she was not under the influence of morphin, and depressed and dulled when under its effects. Her expectation of life was counted in months, if not in weeks. Indeed, she was considered to have reached that stage in her disease when the famous dictum of Osler, "Morphin, more morphin and enough of morphin to allay the violent agony of an incurable carcinoma," was the only therapeutic course left open. Now, what did radiotherapy apparently accomplish in her case? Only a few weeks after therapy was started there was great relief from pain. The dose of morphin was reduced from one-half grain (0.032 gm.) five to six times daily to one-eighth grain (0.008 gm.) three to four times daily. There was great improvement in strength. Her appetite improved. She was no longer

bedridden. Despondency gave place to returned hope. She ceased to be a merely painful burden on her attendants, and there was a fair return to life and its interests. Her general state of well-being in 1924 was better than it was in January, 1923. That this improvement must have been partly due to radiation therapy is fully proven by the local effects on the nodules of the skull. These showed almost complete recession each time under radiation. The other involved areas seemed to show equally favorable effects shortly after roentgen-ray therapy was applied. It is true that the onward course of her illness had not been stopped, but I am convinced that moderate analgesia, palliation and prolongation of life had been achieved by the radiation therapy. By July, 1924, the patient was still in fair general condition, and the use of morphin, which was stopped in November, 1923, had not been resumed.

CONCLUSION

(1) Skeletal metastases may be present at least nineteen years after a carcinoma of the breast has been removed without any evidences of local recurrence.

(2) Osteoplastic skeletal metastases usually pursue a rather slow course and frequently give rise to an inflammatory reaction that may simulate very closely an ordinary benign nonneoplastic process.

(3) Remissions may occur in all forms of carcinoma, and are especially liable to occur in the osteoplastic type of skeletal carcinomatosis.

(4) When a diagnosis of skeletal carcinomatosis is definitely established, it does not invariably mean that the patient is going to succumb to the disease in a few weeks or in a few months. Therefore, one must not immediately resort to the use of morphin and make the patient a miserable habitué long before this becomes absolutely necessary.

(5) Radiotherapy, intelligently and persistently applied and reapplied in skeletal carcinomatosis, is a powerful agent at our command to render analgesia, produce pallation and conduce to prolongation of life not in misery but in comfort.

ABNORMAL ARTERIOVENOUS COMMUNICATIONS, ACQUIRED AND CONGENITAL

IV. THE TREATMENT OF ABNORMAL ARTERIOVENOUS COMMUNICATIONS

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PROGNOSIS

The prognosis in untreated, abnormal arteriovenous communications is uncertain. Some, as a result of infection or increasing hematoma, may lead to such serious consequences as death or gangrene of a part within a few days after their production. When these early complications do not occur, the fistulas usually run a very chronic course, except when they happen to occur between the aorta and the vena cava. There are many cases reported in which an arteriovenous or cirsoid aneurysm had been present for from ten to forty years. There are fifteen cases of such long duration reported in this paper. It is generally true that abnormal arteriovenous lesions of the arms, neck and head are better tolerated than are those of the lower extremity. As a rule, the prognosis is directly dependent on the size of the vessels involved, and on the size of the fistulous opening. Peripheral lesions, such as cirsoid aneurysms, are well tolerated by the body, except when they give rise to local disturbances, such as ulceration or hemorrhage. Fistulas between large vessels frequently give rise to serious cardiac complications, which will shorten the life of the individual. Old arteriovenous lesions may rupture and give rise to serious hemorrhage. This is not uncommon in the case of cirsoid aneurysms or angiomas. Too, gangrene of the part has occurred after a fistula has been present for many years. The occurrence of true aneurysms in the artery proximal to the fistula sometimes occurs. Arteriovenous aneurysms occasionally heal spontaneously. Numerous such cases were reported during the World War, and, of the cases reported in these papers, Case 24 (Paper I) healed spontaneously. Spontaneous healing usually occurs within the first six months if it is going to happen at all. In dogs, experimental fistulas lying close together between artery and vein not infrequently heal. The spontaneous healing of cirsoid aneurysms has been reported by Ferrell,[1] Krackowizer,[2] Orfilla and Chevalier. Angiomas frequently disappear without any treatment. Thrombosis is perhaps the most common cause for the spontaneous healing of angiomas. In angiomas, a truly vascular tumor such as an angiosarcoma or an endothelioma may develop.

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1. Ferrell, H. V.: St. Louis Courier Med. **17**:127, 1887.
2. Krackowizer, E.: New York M. J. **1**:378, 1865.

It is too true that we often fail to appraise properly chronic affections which, while life lasts, are no serious handicap to the individual. In case of such affections, it becames our duty to think of the future, of the days longer our patient may be enabled to live, and not of the day he is living when he comes to the office. It is in such manner that most abnormal arteriovenous communications must be considered, for they are usually chronic affections, often worrying little, but often subtracting days from the end of one's life.

TREATMENT

The nonoperative treatment of arteriovenous aneurysms has proved so unsuccessful and often so disastrous that all efforts along this line have been discarded. It would appear that the treatment by compression, the injection of coagulating fluids, and the use of the galvanopuncture should certainly not be attempted. However, rest, with immobilization of the part and a judicious administration of diet and fluids, would increase the number of spontaneous cures during the first few months after the production of the fistula. Unfortunately, these simple measures are not often used and, if they are used, they are too often not persisted in for a long enough time.

Operative treatment is the best treatment for arteriovenous aneurysms. In this paper, I shall consider only the operative treatment.

Time to Operate.—In some cases, hemorrhage, increasing hematoma (Case 26, Paper I), infection and, very rarely, acute cardiac symptoms make it necessary to operate soon after the injury. Under such conditions, we have no choice. When, however, these complications do not arise, we can choose the time to operate. During the war, it was generally the practice of the French and British to postpone operating on arteriovenous aneurysms for several months, whereas the Germans usually operated within three weeks after the injury. Both Matas [3] and Makins [4] advise waiting for at least two or three months after the injury, unless some of the foregoing complications necessitate an earlier operation. Sharing in this opinion are Bornhaupt, Brentaus, Saigo and Kikuzi. My feeling is that, when possible, the operation ought to be postponed for at least a period of six months following the injury. An exception to this plan may be made in cases of pulsating exophthalmos, in which the eyesight might be endangered by the protrusion.

The advantages derived from delaying operative treatment for several months are: 1. A good collateral circulation develops which permits excision of the fistula without fear of gangrene. 2. The vessels injured become thoroughly healed, and thus their dissection becomes

3. Matas, Rudolph: S. Clin. N. A. **2**:1165 (Oct.) 1922 .
4. Makins, George: Gunshot Injuries of the Vascular System.

easier and safer, especially when a tourniquet cannot be used. 3. Infection of the wound is less likely after the hematoma becomes absorbed and the tissues return to normal. 4. The initial loss of blood at the time of injury becomes fully restored. 5. Some of the cases will heal spontaneously during the first six months, especially if the patient and the part are put at rest. Indeed, some arteriovenous aneurysms have been known to heal spontaneously after having been present for from

Fig. 1 (Case 24, Paper I).—Right subclavian arteriovenous aneurysm 2 months old. At first, signs of a fistula were very marked, and the veins became large rapidly; later, they gradually became less; at the end of six months, the fistula had spontaneously closed.

five to eight years (Makins, Cushing). 6. The evil effects of some arteriovenous aneurysms, particularly those in the upper extremities, may become so mild as not to justify any operative treatment.

The operative treatment of arteriovenous aneurysms may be discussed under the following headings: (1) proximal ligation of the arteries; (2) ligation of the artery proximal and distal to the fistula; (3) ligatures of the vein; (4) quadruple ligation; (5) ligation of the canal

of communication; (6) restoration of the continuity of the vessels by lateral or end-to-end suture, and (7) extirpation.

Proximal Ligation of the Artery.—Although this procedure has for a century been condemned by authors competent to give an opinion, it has taken a long time for surgeons to abandon it. Even at the present time, one occasionally sees reports of cases so treated. The experiences with proximal ligation for arteriovenous aneuryms during the Boer War and the collected statistics of such writers as Matas,[3] Makins,[4] Monod and Vanverts,[5] and Bramann [6] leave no doubt that such treatment is rarely, if ever, justified except in cases of intracranial arteriovenous lesions. Besides failing to cure the aneurysm, proximal ligation of the artery frequently results in gangrene. The explanation for the frequency of the gangrene has been admirably given by Makins. Surgeons long ago expressed the same ideas. For instance, Horner,[7] in discussing the gangrene that followed the proximal ligation of the artery for arteriovenous fistula, said:

> Did not the mortification ensue from its being easier, on the ligature being applied to the femoral artery, for the arterial blood to flow by the anastomoses of the obturator, gluteal or ischiatic arteries into the circumflex—thence into the sac, and return thence by the femoral vein, than flow to the foot and parts below the groin? The freedom of this anastomotic communication with the sac was proved, by the aneurysm continuing, though the main current of blood through the femoral artery was cut off, as proved by the necropsy. Would it not, therefore, be always proper to secure in every direction the arterial trunks, primary and collateral, communicating with a varicose aneurysm, so as to force the blood downwards to the limb below, and thus prevent the possibility of its returning to the vein without a complete circulation?

Strohmeyer (1844) gave a similar explanation for the gangrene, and suggested that an accidental inclusion of the vein in the ligature of the artery would be a good thing. Stimson [8] and Curtis [9] were others to express the same ideas about the causation of the gangrene. It may be of interest to note that Erskine Mason (1877), believing that all proximal ligations of the external iliac and femoral arteries for arteriovenous aneurysms had failed to effect a cure, gave a patient ether anesthesia continuously for eighteen and a half hours, during which time he compressed a femoral arteriovenous aneurysm. Improvement resulted.

Ligation of the Artery Proximal and Distal to the Fistula.—This procedure, though much less dangerous than simple proximal ligation,

5. Monod and Vanverts: Rev. de chir. **42**:729, 1910.
6. Bramann, F.: Arch. f. klin. Chir. **33**:1, 1886.
7. Horner, W. E.: Am. J. M. Sc. **1**:74, 1841.
8. Stimson, L. A.: Am. J. M. Sc. **87**:325, 1884.
9. Curtis: Am. J. M. Sc. **101**:142, 1891.

possesses the same faults. Intermediate branches may keep the fistula alive and serve to shunt the arterial blood into the veins without forcing it through the capillaries. This procedure should not be used when it can be avoided.

Ligatures of the Vein.—These alone have rarely been employed.

Quadruple Ligation.—This procedure has been widely employed, and has yielded very good results. It was used a great deal during the World War. It is obvious that all branches arising from the fistula bearing segment of vessels included between the four ligatures should, if possible, be ligated. Failure to secure these branches is the explanation for the failures of this procedure to cure arteriovenous aneurysms, and is probably the cause for the grave circulatory disturbances of the part beyond the fistula in some cases.

Ligation of the Canal of Communication.—This is rarely possible. It has been done by Cranwell,[10] Weigel,[11] Selbert, Berkeley[12] and Bonney, and was performed in Case 25 (Paper I) of this series. This procedure plus either a ligation of the artery or vein was performed by Van Ischmoot, Boddaert and Vercauteren, Westergaard and Erdmann. Even ligation of the canal of communication is open to the criticism that the artery at the site of the fistula or in the diseased proximal portion may develop a true aneurysm. Something of this nature happened in Delbert's[13] case. It is doubtful if this procedure should be employed, even when possible.

Restoration of the Continuity of the Vessels Either by Lateral or End-to-End Suture.—As has been pointed out by Matas,[3] this procedure has been employed mainly on cases of very recent origin. The Germans, who usually operate within three weeks, prefer this method. Though probably not necessary (if both artery and vein are tied), this operation, in early cases, is not open to much criticism. The danger of restoring a diseased artery to normal function and of air or blood emboli exists to only a small degree. In old cases, my clinical and experimental work do not seem to justify restoration of the vessels. The development of an abundant collateral blood supply makes the operation unnecessary. It is doubtful if the badly degenerated artery should be restored to normal function. Finally, the danger of blood and air emboli, when these large dilated vessels are opened and restored, under a tourniquet, is a real danger. When the aneurysm is opened, blood wells out from, and air goes into, the large vessels, permitting the trapping of air and blood clots in the vessels. In Heuer's case, the

10. Cranwell, J.: Rev. de chir. **34**:817, 1906.
11. Weigel: München. med. Wchnschr. **62**:1119, 1915.
12. Berkeley, C., and Bonney, V.: Brit. M. J. **1**:753 (May 27) 1916.
13. Delbert, Pierre: Thèse de Paris, 1888-1889, No. 151.

result was a pulmonary infarcation which caused death. Halsted's patient developed pulmonary infarcts, but recovered (Cases 9 and 10, Paper I). Even when the artery is restord, it is doubtful if the vein should be restored under any circumstances.

Extirpation.—Although a mastery of modern surgical technic makes vascular suturing relatively simple, the results of extirpation have been so good that I believe it should remain the procedure of choice in old cases, and probably in recent cases. In Case 24 (Paper I), extirpation of the femoral vessels was performed forty-eight hours after the injury and when the tissues of the thigh were so distended and impregnated with extravasated blood that it was not possible to recognize them. Circulation of the foot remained good, and a pulse returned in it on the ninth day. In another case, extirpation of the subclavian vessels was done three weeks after the injury without apparent circulatory disturbance to the arm. More convincing proof of the relative harmfulness of excising parallel large arteries and veins is a recent case of gangrene of the toes and part of the foot due probably to arteriosclerosis. As amputation above the knee seemed inevitable, I first excised a portion of the femoral artery and vein in Hunter's canal, and also the long saphenous vein. To my surprise the foot showed marked improvement for a period of a week. The swelling subsided; the foot became warmer, and the gangrene did not progress. During this time, the veins below the knee were distended. After a week, these dilated veins disappeared; the pain returned, and the gangrene and infection began to spread. Amputation became necessary.

The value of extirpation for arteriovenous aneurysms has long been known. Before the Boer War, when so many soldiers developed gangrene as a result of proximal ligation of the artery, some good authorities had reviewed the literature and concluded that extirpation gave the best results.[14] The excision of artery and vein for arteriovenous aneurysms is an entirely different proposition from that of a simple arterial aneurysm, in which extirpation of the aneurysm should be condemnned unless by so doing the artery may be sutured.

In some cases, the location of the aneurysm makes it obviously unwise, if not impossible, to attempt extirpation. The intracranial aneurysms, particularly the anastomoses between internal carotid artery and cavernous sinus leading to pulsating exophthalmos, fall into this group. Rhodes[15] reports fourteen different methods that have been employed in the treatment of this condition. Chief among these procedures have been ligations of the common and internal carotid arteries, and of the supra-orbital vein. Often, combinations of these procedures

14. Murray and Page, F.: Lancet **1**:1488, 1899. Page, F.: Lancet **2**:1164, 1900.

15. Rhodes, G. B.: Ann. Surg. **63**:389 (April) 1916.

have been used. By all procedures, about 50 per cent. of the cases have been cured, and 20 per cent. have been relieved. Undoubtedly, most of the cures have been the result of a thrombosis at the site of the fistula. Attention is drawn to a new procedure employed in two cases reported in this series; namely, a complete ligation of the external carotid artery by a heavy silk ligature, and of the common carotid by a metallic band (Fig. 2).

It seems obvious to me that at least two arterial ligations are necessary in order to secure a maximum diminution of the arterial flow

Fig. 2 (Case 16, Paper I).—Pulsating exophthalmos successfully treated by the method illustrated in Figure 3.

through the fistula. For instance, if the common carotid artery alone is ligated, there remains a free communication between the internal and external carotid arteries through which blood could flow in either direction. Likewise, if the internal carotid artery alone is ligated, anastomoses between the branches of the external carotid artery and the intracranial vessels (particularly about the eye) would tend to preserve a circulation through the fistula. Ligating both external and internal carotid arteries would check the arterial circulation as effectively as the method advocated, but the latter procedure has these advantages: the

internal carotid is a little more difficult to isolate than is the common carotid, and, in case of cerebral disturbances, a band could more easily be removed from the common than from the internal carotid artery.

Although ligation of the internal jugular vein at the same time as the arterial ligation, for pulsating exophthalmos, has rarely been done (Rhodes found one case), the recent studies of Makins,[4] Halsted, Reichert and myself [16] would indicate that such a procedure ought to yield the highest percentage of cures and reduce the postoperative cerebral disturbances. For it would further lessen the circulation through the fistula, and would tend to obviate the anemia of the brain by preventing a too rapid shunting of the arterial blood, by way of the

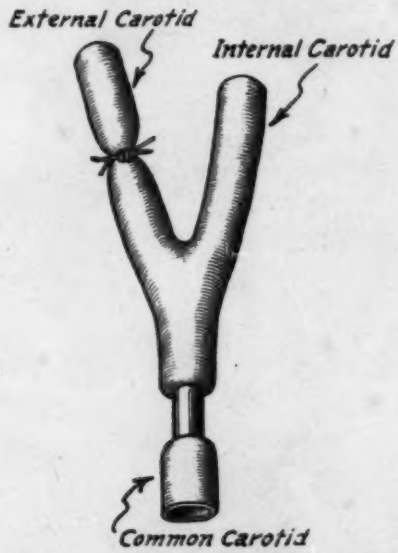

Fig. 3.—Ligation of the common and external carotid arteries to treat pulsating exophthalmos. If necessary, the band may be removed from the common carotid artery.

fistula, back to the heart. In addition to the operations on the carotid vessels and jugular vein, it might also be advisable to ligate the large supra-orbital veins.

The employment of these venous ligations, in addition to the arterial, is mentioned in the preceding paragraph because I believe that such a procedure is logical and sound, and that a surgeon would be justified in using it. However, the reader is reminded that the future results of surgeons who choose the simultaneous venous and arterial ligations for pulsating exophthalmos will have to determine the true merits of

16. Halsted, W. S.; Reichert, E. L., and Reid, M. R.: Tr. Am. Surg. A. **40**:160-167, 1922.

the procedure. For the present, I feel safe in saying that ligation of the external and common carotid arteries is good, and that the simultaneous ligation of the internal jugular vein (probably also the supraorbital vein) appears to me to be logical.

THE TREATMENT OF CIRSOID ANEURYSMS

Surgeons long ago recognized the fact that the simple ligation of large arteries proximal to a cirsoid aneurysm rarely ever sufficed to cure. They were generally agreed that a direct attack on the aneurysms, often preceded by the proximal arterial ligations, offered the best hope for a cure. When we consider the free anastomoses between the peripheral arteries, particularly on the scalp, there is little wonder that the arteriovenous anastomoses, which are the cause of the cirsoid aneurysms, should remain active, and that the other small feeding arteries

Fig. 4.—Method of treating cirsoid aneurysm by means of strangulation with pins; often successfully employed during the first half of the nineteenth century. (From Gross's Textbook of Surgery.)

should soon enlarge following the ligation of large proximal arteries. Stanley [17] commented that the arteries probably dilate in order to supply the demands of the diseased structure, and that, consequently, if cut off, they will soon be replaced by others.

Travers (1809) and Dalrymple (1813) ligated the carotid arteries for cirsoid aneurysm of the scalp. In 1829, the number of failures to cure by simple ligation of the carotid artery had grown so large that Brodie [18] strangulated the aneurysmal mass in addition to ligating the main feeding vessels. Barton,[19] in this country, employed the same procedure, also successfully, just three months after Brodie. The number of men who disapproved of ligating the proximal arteries alone rapidly increased. There are so many that only a few need be mentioned—Liston (1836),

17. Stanley: M. Times & Gaz. **7**:244, 1853.
18. Brodie, B. C.: Tr. Med. Chir. **15**:177, 1829.
19. Barton: Am. M. J. **16**:322, 1835.

Van Buren (1887), McBurney (1887), Wernher (1876), A. W. Smith (1873), Ferguson (1885), Billroth and Mason Warren.[20] Pemberton [21] concluded that ligation of the main trunks leading to the aneurysm, together with an excision of the "tumor," was the surest means of curing the condition. He disapproved of ligations of the main vessels alone. When, along with ligations, excision has not been possible, other adjuncts, such as pressure over the aneurysm, the application of caustics, the injection of astringents, boiling water, etc., and the use of strangulating pins, have frequently been effective in causing an occlusion of the arteriovenous anastomoses.

In extensive cirsoid aneurysms of the extremities, particularly those in which the anastomoses are situated within the long bones, amputation, the ligation of the main vessels plus the injection of fluids, under a tourniquet, at the site of the anastomoses might effect a cure. At this point, it may be of interest to append an abstract of J. Mason Warren's case.

A girl, aged 19, of a delicate constitution, when 2 years old, had received an injury from a stone in the palm of the hand, and very shortly afterward a small pulsating tumor appeared there. About five years before the operation, she presented herself at the hospital. At this time, a large tumor occupied the whole hand, held as it were in the palm. It was firm at some points, soft and pulsating at others, and seemed to have made its way backward, so as to give the idea that all the bones of the hand had been flattened and that they formed a shell to it. On compression, the tumor gave a powerful aneurysmal thrill, and in some parts of it the blood seemed to be contained in large aneurysmal sacs; at others, arteries the size of the carotid could be detected. Amputation was advised as the only resource, but was declined. A cast was made of the arm and hand at that time. In addition to the tumor in the palm of the hand, there was also a supplementary tumor, quite firm to the touch, and without pulsation, reaching up the whole forearm under the muscles.

Last spring, the patient again presented herself to Dr. Warren, the tumor having more than doubled in size, and the swelling on the forearm having increased in a correspondent manner. At this time, also, a distinct aneurysmal thrill attended the pulsation of the brachial artery, and the surrounding veins were in a highly varicose state. Auscultation of the tumor of the hand gave a sound like the noise of the machinery of a factory. The arm was now quite unwieldy, and at times very painful, and the disease was rapidly increasing. The surgeons of the hospital, in consultation, decided that amputation was the only means of relieving the patient, but they considered that there was a possibility of meeting with erectile tissue in the arm. The patient was quite timid, and unwilling to encounter any more than the ordinary danger from an amputation. She therefore again returned home, but, later, the pain being so severe and the tumor making advances, she submitted to the operation by the advice of her physician, Dr. Jones. In making the compression, it was deemed necessary to place a tourniquet quite high on the limb, and screw it up so as to compress forcibly the whole limb. Nearly twenty vessels, both arteries

20. Warren, J. M.: Boston M. & S. J. **57**:528, 1858.
21. Pemberton, Oliver: Lancet **1**:516, 1860.

and veins, required ligature, as it was soon found that the veins carried arterial blood and were disposed to bleed. The quantity of blood lost in the operation was extremely small, on account of the very effectual way in which the compression was applied.

The day after the operation, there was a great reaction; and this was so violent, the following day, that it was found necessary to take blood from the patient. This was done, with relief. The whole limb, however, shortly became fiery red, and a diffuse, painful swelling appeared in the neck, just above the clavicle. In a week or ten days, this subsided, but one morning it was observed that the breast had suddenly become puffed up, and a day or two after, a great quantity of pus was discharged by an opening and a counteropening.

The patient, after long convalescence, went home, well. During the whole of the after treatment, there was no hemorrhage from the stump, and no evidence that any erectile tissue remained.

The arm, which was exhibited, had been very beautifully injected by Dr. Bigelow, and a careful dissection had been made of it by Dr. Hodges. The wax injection was thrown into the veins, and was retained by the brachial artery. The veins of the arm and hand were greatly dilated, and formed a beautiful basketwork around the bone; in the palm of the hand, they communicated freely with the arteries, which were dilated so as to form what might be called large sinuses. The solid part of the round tumor in the hand and forearm was formed of condensed and infiltrated cellular tissue.

The specimen was presented by Dr. Warren to the Warren Museum.

The lesson to be learned from this study of cirsoid aneurysms is that they should be excised early, before the arteriovenous anastomoses have led to such formidable vascular changes that excision becomes too dangerous or even impossible. In Case 27 (Paper I), excision of the fistula was easily performed, whereas a delay in treatment would soon have resulted in a difficult lesion to deal with.

CIRCULATORY BALANCE

For several centuries, surgeons have been carefully taught how to ligate large arteries without injuring the accompanying vein. This idea of preserving the vein is so ingrained in our profession and is yet so commonly executed that it may be worth while to call attention to some recent experimental work and clinical studies which indicate that it is wrong; especially as six cases, reported in this series of papers, add further support to the rapidly growing belief that, when a large artery is ligated, the accompanying vein should also be ligated.

Our clinical and experimental work so well substantiate the views expressed by Sir George Makins that I quote at length from him:

In preparing a former contribution to the surgery of wounded arteries, I was much struck by the observation that proximal ligature of the femoral artery, in cases of arteriovenous aneurysm, was followed in a large proportion of instances by gangrene of the limb, while excision of the implicated segments of both artery and vein gave consistently good results. An explanation

of this apparent inconsistency will be found below, as also further considerations which led me to conclude that when an artery needs to be tied, the satellite vein should be occluded also.

It is to be regretted that John Hunter himself did not write the paper describing his operation of proximal ligature and the grounds upon which he was led to undertake it. In at least one of the cases described in the paper by Sir Everard Home, possibly in the first three, both the femoral artery and vein were included in the ligature; in the fourth, we are definitely told that the artery only was included. From that period onwards, surgical opinion has been definitely to the effect that the greatest care should be taken, when occluding a main artery, to avoid all injury to the vein. In fact, every operation for the ligature of an artery has been so devised that the aneurysm needle is passed in a direction away from the vein in order to minimize the risk of injury to that vessel, not alone to avoid the technical inconvenience of immediate hemorrhage, but also with the definite object of preserving the venous circulation intact.

Observations of a large number of coincident wounds of large arteries and veins has in no way endorsed the view that simultaneous occlusion of both artery and vein exercises any deleterious influence on the subsequent collateral arterial circulation and the vitality of the limb. In support of this statement, a few examples illustrating the innocuous nature of operations for the occlusion of veins in general may be first given. Operations for the cure of varicose veins have demonstrated the ease with which a compensatory balance is attained when the blood is diverted from the larger channels. Occlusion of the internal jugular and other large venous trunks, effected in order to prevent the diffusion of septic emboli, has not given rise to obvious permanent trouble. As is well known, also, occlusion even of the vena cava by surgical methods has been survived, and the capacity of the venous circulation to maintain itself by compensatory changes, which is seen when this vessel undergoes obstruction by thrombosis, is a familiar experience.

In a very considerable proportion of gunshot injuries to large arterial trunks, the neighboring vein is contused and becomes thrombosed, and this has not been shown to give rise to increased risk of gangrene of the limbs. Ligature of the common carotid artery together with the internal jugular vein en masse has been performed in cases of emergency without increased risk of the development of the cerebral anemia and softening so often a consequence of ligature of the artery alone. Further, where simultaneous ligature of both artery and vein in other parts of the body has been obligatory on account of wounds of both vessels, untoward events have not been observed.

Evidence exists, moreover, that under certain conditions simultaneous occlusion of both artery and vein is a preferable procedure. The first example, not an unmixed or simple one, may be sought in the results observed to follow the application of a single proximal ligature to the artery in cases of arteriovenous aneurysm or aneurysmal varices of the femoral vessels. In patients so treated during the South African War, gangrene of the limb followed in more than 50 per cent. of the cases. The frequency of this accident finds a simple explanation if we consider what actually results from the operation. The main vessel being occluded and the direct arterial pressure from behind being abolished, blood which has been carried by the arterial collaterals to the distal portion of the injured trunk instead of passing to the peripheral circulation, takes the course of least resistance backward into the vein through the arteriovenous communication, and thus the limb practically bleeds to death, much in the same way as if the distal end of the wounded artery opened on the surface

of the limb. Hence, the comparative safety of removal of the communication en masse and occlusion of all four openings by ligature which has been confirmed by numerous operations during the present war.

A more striking example is offered by the result of ligaturing the popliteal vein alone for the treatment of senile gangrene of the foot. W. A. Oppel, ascribing the good results occasionally observed to follow arteriovenous anastomosis for the cure of this condition to control of the venous circulation and consequent rise in the blood pressure of the limb, was led to substitute simple occlusion of the popliteal vein to produce the same effects. In six cases thus treated, the extremities were seen to recover not only their warmth and color without the development of edema, but also a certain degree of hyperemia of the feet and toes.

On these and other grounds, it must be admitted that the balance of the collateral circulation is likely to be more efficiently maintained if the vessels which carry it on more nearly correspond in size and consequent equality in the blood pressure and rate of flow. The elimination, in fact, of the capacious main vein is a real advantage, since this for the time affords a too ready channel of exit for the diminished arterial supply, as well as an undesirable reservoir for stagnation.

These considerations have led me not only to regard obligatory simultaneous occlusion of a main artery and vein as a negligible factor in the risk of gangrene of a limb, but to hold, further, that the procedure is preferable whether the vein be wounded or not; the result of the combined procedure being to maintain within the limb for a longer period the smaller amount of blood supplied by the collateral arterial circulation, and hence to improve the conditions necessary for the preservation of the vitality of the limb.

M. van Kend tested the accuracy of the above conclusions as to the rise of blood pressure at the laboratory of the Ocean Ambulance at La Panne by some experiments on animals, and made the following remarks in his observations at the Interallied Conference of Surgeons, held in Paris in May, 1917:

"In carrying out a series of experiments made with the object of determining the indications and the physiological basis for transfusion of blood, I have had the opportunity of measuring the blood pressure in limbs of which the main artery had been ligatured. The blood pressure was taken successively after the artery alone had been tied and again when ligature of the vein had been superadded. My observations confirm the view that has been expressed by Sir George Makins; in fact, plethysmographic tracings demonstrate clearly that a slight rise in the blood pressure in the limb follows the application of a ligature to a main vein, after previous ligature of the artery.

"It appears, then, from the standpoint of the physiologist, that to leave the main vein viable after occlusion of the main artery of a limb diminishes what may be called the residuary blood pressure maintained by the collateral circulation. If the contribution of the collateral circulation is allowed to remain with the main vein intact, it is natural that the residuary blood pressure should fall. If this view be adopted, ligature of the vein as well as the artery should be recommended in order to retain the blood supplied in longer contact with the tissues. Thus the most satisfactory conditions for the maintenance of the nutrition of the organs are provided, because the obstacle to the return circulation provided by ligature of the vein retains the blood for a longer period in the member."

After discussion of the question at the meeting, the following conclusion was adopted: Contrary to what has until now been believed, simultaneous

ligature of both artery and vein when both vessels have been wounded does not give rise to increased risks of gangrene; in fact, it diminishes them. Facts tend to prove, even when the wound is limited to the artery, that simultaneous occlusion of the unwounded vein is to be recommended.

Maj. Hamilton Drummond has kindly furnished me with a note regarding some investigations which he made on this subject in the case of the visceral vessels. Loops of the small intestine of the cat and of the colon of the Belgian hare were made use of. After a careful study made by means of barium injections and roentgen-ray photographs to determine the number of vessels which should be ligatured in order to avoid error from leaving too free an anastomotic supply, the following experiment was made six times on cats' intestines.

A loop of ileum towards the cecal end was drawn out of the abdomen, and the arteries and veins supplying about 5 inches of the gut were ligatured, cutting off the total macroscopical blood supply to that portion. The loop was returned into the abdomen, and a second loop, about 6 inches higher, was delivered and devascularized by ligature of the artery alone.

Of six experiments performed upon the cat, in three a definite ring of gangrene developed in the middle of the segment of bowel which had been deprived of its arterial supply alone, while the segment treated by simultaneous ligature of artery and vein showed little or no change. In one case in which the animal was killed while still looking in good health, twenty-four hours after ligature of the vessels, the segment treated by ligature of the arteries only showed more serious changes than the segment treated by simultaneous ligature of artery and vein. Of the remaining two cases, one showed no change at all, consequent upon the fact that too short a segment of the bowel had been deprived of its blood supply, while the result in the sixth case was complicated by the development of an acute volvulus.

He further states: "Whenever it is determined to ligature the common carotid or its branches, simultaneous occlusion of the vein should always be a part of the operation. It has proved certain that occlusion of the satellite vein is advisable in dealing with the arteries of the extremities, and if the explanation be found in the reduction of the degree of anemia consequent on interference with the arterial supply it is clear that the procedure is doubly advisable in the case of one of the chief sources of the blood supply of the brain."

The experimental work of van Kend, Halsted and Brooks and the clinical observations of von Oppel [22] have yielded a plausible explanation for Makin's conclusion. All these workers have demonstrated that the peripheral blood pressure in the limb of an animal is higher after the simultaneous ligation of its main vein and artery than it is after the ligation of the artery alone. Brooks and Martin [23] believe that this increase in the peripheral blood pressure is the principal beneficial result of ligating the vein. They do not agree with Makins that the good effect of simultaneously ligating the vein and artery is to maintain within the limb for a longer priod of time the smaller amount of blood supplied

22. Von Oppel, V. A.: Centralbl. f. Chir. **2**:1241, 1913.

23. Brooks, Barney; and Martin, K. A.: Simultaneous Ligation of Vein and Artery, J. A. M. A. **80**:1678 (June 9) 1923.

by the collateral circulation. Our observation of completely stagnant blood in many of the peripheral capillaries in Case 17 (Paper I) supports the views of Brooks.

Regardless of these reasons there is now sufficient clinical evidence for the belief that, in operations on large arteries, we should strive to establish a circulatory balance in the parts supplied by those arteries, by treating the veins similarly to the way in which the arteries are treated. This principle of therapy is especially applicable to the treatment of arteriovenous aneurysms in which the venous bed becomes enormously dilated as a result of the fistula. In such cases, we may learn that it is advisable to excise more veins than the one corresponding to the excised artery. Indeed, it may be that the dilation of the arteries and the enormous development of collateral blood vessels, as a result of arteriovenous fistulas, are, in part, Nature's effort to establish a circulatory balance by making the arterial bed commensurate with the large venous bed.

Since the venous bed is much more readily adaptable than the arterial, the lack of a circulatory balance usually occurs on the arterial side. Hence it is that the ligation of a large vein does not necessitate the ligation of the corresponding artery. In a case of a femoral arteriovenous aneurysm forty-eight hours old, I deliberately excised the saphenous vein, in addition to excising the femoral artery and vein. For about ten days, the superficial veins of the leg remained distended, even though the leg was elevated. Although the circulation of the foot remained good, it is likely that for this period of time there was an overbalance on the arterial side. In extensive venous thromboses, the arterial overbalance is probably responsible for the edema. If this is borne in mind, proper surgical treatment of the arteries may prove to be of great help in persistent cases of edema due to venous thrombosis.

Arteries are much more prone to endarteritic and arteriosclerotic changes than are the veins. Such changes diminish the function of the arterial bed without decreasing the carrying capacity of the venous bed. Thus, a lack of balance occurs on the arterial side. The good results, reported by von Oppel and others, in senile gangrene from ligating the main vein are probably due to a restoration of a more or less normal circulatory balance. In Raynoud's gangrene and other gangrenes not due to rigid arterial walls, the periarterial sympathectomy tends to establish a normal balance by causing the arterial bed to dilate and thus increasing its blood carrying capacity.

In the treatment of fistulas that result in cirsoid aneurysms and angiomas, it will rarely be necessary to consider the maintenance of a vascular equilibrium, for they are usually situated peripherally and are attacked directly, except when located within the skull.

OPERATIVE TECHNIC

No operations require a more rigid technic than do operations for aneurysms. The operative procedures are often very long; the consequences of infection are disastrous. Most careful cleansing of the skin, gentle handling of tissues and absolute hemostasis should be observed in these operations. In addition, we have usually protected the wound from the skin by covering the field of operation with collodionized China silk (Fig. 5). Elevation of the field of operation, particularly in dealing with angiomas and cirsoid aneurysms, is often helpful for it makes the tendency to bleeding much less.

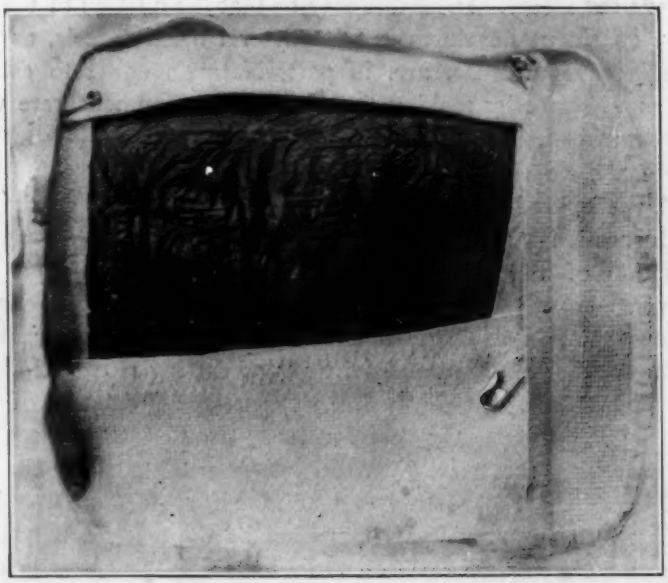

Fig. 5.—Field of operation covered with collodionized China silk; incision is made through the silk, which remains adherent to the skin.

In all our operations, we have employed silk for ligatures and sutures because we have found it safer and less irritating to wounds than catgut. Certainly, large arteries should be tied with silk or some unyielding material that will hold the ligation absolutely stationary until Nature repairs with scar tissue the arterial wall, which always dies under any ligature.

The method of approaching an arteriovenous aneurysm must vary with its position. When the operation can be performed under a tourniquet, immediate exposure of the fistula by incision through the venous or arterial wall, or an intermediate aneurysmal sac, will greatly facilitate the operation. The value of such a procedure was long ago recognized

by James Syme [24] and Annandale.[25] It has been practiced by Kikuzi, Saigo, Anderson,[26] Keyes,[27] Curtis,[9] Monod and Vanverts,[5] Makins,[4] Matas [3] and many others. The transvenous approach to the fistula, described by Bickham and often employed by Matas and himself, is known as the "Matas-Bickham method." After exposing the fistula, one can more readily either restore the vessels, ligate all vessels communicating with the fistula, or, preferably, excise both vessels at the site of the fistula.

In the postoperative treatment, it is important to elevate the limb, apply heat and use frequent gentle massage directed toward the heart. These measures were very helpful in Case 24 (Paper I), when for a time a slight overbalance was established on the arterial side.

SUMMARY AND CONCLUSIONS

1. Arteriovenous aneurysms occasionally heal spontaneously; cirsoid aneurysms rarely heal spontaneously.

2. When it is possible to wait, arteriovenous aneurysms should not be operated on earlier than from three to six months after the injury. In this time, healing may occur, and an abundant collateral circulation will develop.

3. Cirsoid aneurysms should be treated as soon as a diagnosis is made.

4. In general, extirpation of the involved vessels yields the best results in the treatment of abnormal arteriovenous communications—arteriovenous aneurysms, cirsoid aneurysms and angiomas. I feel that this procedure is preferable to all others when an arteriovenous aneurysm has been present for any length of time; whereas, in very early cases restoration of both vessels or of the artery, when possible, may be desirable.

5. In cases of pulsating exophthalmos, the external carotid artery should be ligated and the common carotid occluded by a band. The jugular vein should also probably be ligated, though this has not generally been done.

6. In all operations on large arteries, an effort should be made to establish a normal vascular equilibrium in the part supplied by those vessels. This probably means that, when a large artery is tied, the accompanying vein should also be ligated.

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24. Syme, James: Edinburgh M. J. **31**:66, 1829.

25. Annandalé, cited by Matas in Keen's System of Surgery, p. 281.

26. Anderson, W. N.: Rupture of an Aortic Aneurysm into the Superior Vena Cava, J. A. M. A. **81**:1877 (Dec. 1) 1923.

27. Keyes, E. L.: Virginia M. Month. **8**:644, 1881-1882.

THE SECRETION ANTECEDENTS AND MITOCHONDRIA IN PATHOLOGIC THYROIDS

A THEORY OF THE MODE OF SECRETION IN THE THYROID GLAND *

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That increased basal metabolism is associated with increased thyroid activity is well known and requires no comment here. It has, however, been observed that the pathologic picture in adenomas of the thyroid does not always correspond to the clinical state.[1] In exophthalmic goiter there is quite general agreement as to the pathologic changes present in the various stages of the disease.[2] The pathology of simple goiter and of fetal and simple adenomas is quite clear.[3]

It has long been known that certain nonexophthalmic goiters were accompanied by toxic symptoms. Plummer,[4] in reviewing the cases at the Mayo Clinic, found that 23 per cent. of the nonexophthalmic goiters were toxic, and presented either one or the other of two definite clinical pictures: one type resembling exophthalmic goiter, and the other having

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1. Goetsch, E.: Newer Methods in the Diagnosis of Thyroid Disorders, N. Y. State J. M. **18**:259 (July) 1918.

2. Lewis, D. D.: The Pathologic Anatomy of Exophthalmic Goiter, Surg., Gynec. & Obst. **3**:476, 1906. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158 (Oct. 5) 1907. Wilson, L. B.: The Pathologic Changes in the Thyroid Gland as Related to the Varying Symptoms in Graves' Disease, Am. J. M. Sc. **136**:851, 1908; The Pathologic Relationships of Simple and Exophthalmic Goiter, Surg., Gynec. & Obst. **8**:588, 1909; Notes on the Pathology of Simple and Exophthalmic Goiter, M. Rec. **84**:373, 1913; The Pathology of the Thyroid in Exophthalmic Goiter, Am. J. M. Sc. **146**:781, 1913. Marine, D., and Lenhart, C. H.: The Pathologic Anatomy of the Human Thyroid Gland, Arch. Int. Med. **7**:506 (April) 1911; Pathologic Anatomy of Exophthalmic Goiter, ibid. **8**:265 (Sept.) 1911. Kocher, Albert: Die Histologische und chemische Veränderung der Schilddrüse, Virchows Arch. f. path. Anat. **208**:86, 1912.

3. Wolffer, A.: Ueber die Entwicklung und den Bau des Kropfes, Arch. f. klin. Chir. **29**:1, 1883. Bloodgood, J. C.: Cysts of the Thyroid Gland, Surg., Gynec. & Obst. **1**:113, 1905; Adenoma of the Thyroid Gland, ibid. **2**:121, 1906. Wilson, L. B.: A Study of the Pathology of the Thyroids from Cases of Toxic Nonexophthalmic Goiter, Am. J. M. Sc. **147**:344, 1914. Wilson (Footnote 2, fourth and sixth references). Marine and Lenhart (Footnote 2). Goetsch (Footnote 1).

4. Plummer, H. S.: The Clinical and Pathologic Relationship of Simple and Exophthalmic Goiter, Am. J. M. Sc. **146**:790, 1913; The Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, J. A. M. A. **61**:650 (Aug. 30) 1913.

a predominance of cardiac symptoms. Wilson [5] reviewed the glands of the cases studied by Plummer, and found that those presenting a picture resembling exophthalmic goiter were about equally divided between regenerating colloid adenomas and fetal adenomas. Of those toxic nonexopthalmic goiters which clinically did not resemble exophthalmic goiter (cardiac type), 64 per cent. were pathologically simple goiters with adult parenchyma.

Goetsch,[6] in 1916, reported that the mitochondria were definitely increased in the cells of toxic adenomas, and enormously increased in the cells of exophthalmic goiters. In 1918, he reported mitochondrial studies on twelve simple goiters, fifty exophthalmic goiters and 125 adenomas. In this large series, he found that, in simple colloid goiters without toxic symptoms, few or practically no mitochondria were present, while, in hypertrophy with symptoms, they were present in moderate numbers; in adenomas with symptoms, they were present in excessive numbers, and in exophthalmic goiters they were present in enormous numbers. In other words, the toxicity of the thyroid varied directly with its mitochondrial content. He concluded that a study of the mitochondria was the only reliable method of determining the state of activity of certain pathologic thyroids, as, in adenomas, every type of growth and degree of hyperplasia might be present and the symptoms still vary from hypothyroidism to hyperthyroidism.

The foregoing conclusions are important, and demand consideration by all who are interested in the thyroid. They stand alone, and have neither been confirmed nor denied. Goetsch's observations were particularly interesting to me because I have for some years been interested in the question of the functional significance of mitochondria, and have, at various times, attempted to find a solution to the problem, but always with negative results. Consequently, I decided to study a series of pathologic thyroids in the hope that I might confirm Goetsch's observations, and at the same time gain some light on the question of the functional significance of the mitochondria. I am indebted to the surgical and pathologic departments of the Peter Bent Brigham and the Massachusetts General hospitals for permission to collect the material directly after its removal at operation, and to the medical departments of these hospitals for the basal metabolism determinations.

In studying the pathologic cytology of a gland, it is necessary to inquire rather minutely into what is known regarding its normal mode of secretion. In reviewing the literature on the thyroid, one is struck by the utter lack of agreement among the different investigators as to

5. Wilson (Footnote 3, fourth reference).

6. Goetsch, E.: Functional Significance of Mitochondria in Toxic Thyroid Adenomata, Bull. Johns Hopkins Hosp. **27**:129 (May) 1916.

its normal mode of secretion. It is not even known whether the cells secrete into the follicles or directly into the circulation, and whether the colloid is the normal secretion or a storage product. Horne [7] reported occasional colloid droplets in the lymphatics of pathologic human thyroids. But subsequent observers have questioned his and other similar findings on the basis that vessels in other organs often contain hyaline masses that might be interpreted as colloid.

Bensley [8] states that our earliest knowledge as to the origin of the interfollicular colloid is due to Biondi,[9] who showed that this substance is a true product of the secretory activity of the thyroid epithelial cells, as he found globules of a similarly staining substance in the cells themselves. Of the process of secretion, he said:

> The cells of the thyroid gland produce the colloid, since one can see in them little globules having the same microchemical reactions. The vesicle has a tendency to increase in size partly by multiplication of the epithelial cells, partly by increase of the colloid; after filling itself, the vesicle discharges into the nearest lymphatic vessels; finally the collapsed vesicle disposes itself in the form of a number of little acini which repeat the process.

Langendorff [10] studied the thyroids of various animals at different ages. He studied the colloid microchemically, and found that it became swollen and transparent when treated with acids and was dissolved by strong alkalis. It gave positive xanthoproteic, biuret and Adamkiewicz's tests, and a positive Millon's test after one hour or more in the oven. Mucin was not present. Osmic acid caused it to turn dark. The colloid was not dissolved in alcohol in forty-eight hours. He described two types of cells in the walls of the acini, which he termed chief cells and colloid cells. The chief cells, which constituted the main mass of the thyroid epithelium, possessed a granular cytoplasm. The colloid cells differed from the chief cells in that their protoplasm was homogeneous and hyaline, their nuclei shrunken, and the cell borders poorly defined. They were tinted dark by osmic acid, and stained deeply with all stains that stained the colloid. All transitions between chief and colloid cells were noted. Occasional hyaline spherules (colloid of Biondi) were noted in the cells, but were too rare to be of much consequence.

The colloid cells, which were the functioning cells, were scattered irregularly through the gland. They formed the colloid through meta-

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7. Horne, R. M.: On Colloid in the Lymphatics and Blood Vessels of the Thyroid in Goiter, J. Anat. & Physiol. **27**:161, 1893.

8. Bensley, R. R.: The Normal Mode of Secretion in the Thyroid Gland, Am. J. Anat. **19**:37 (Jan.) 1916.

9. Biondi, D.: Contribution à l'étude de la glande thyréoïde, Arch. ital. de biol. **17**:475, 1892.

10. Langendorff, O.: Beiträge zur Kenntniss der Schilddrüse, Arch. f. Anat. u. Physiol., Supplement, 1889, p. 219.

morphosis of their cytoplasm, and passed it into the follicles, whence it passed back through the follicle walls into the lymphatic spaces. He did not state whether these colloid cells degenerated after secretion or returned to the condition of chief cells.

Wyss [11] poisoned cats and dogs with pilocarpin, and found the thyroids large, turgid, and filled with blood. On microscopic examination, the cells were larger and the nuclei less apparent. The free ends of the cells were prolonged into processes which were continuous with colloid masses, and between these processes were brilliant spherules of apparently fluid nature and colloid-like droplets.

Andersson [12] injected pilocarpin into cats, dogs, rabbits and rats, and studied the thyroids at various intervals after injection. He confirmed Wyss's observation as to the engorgement of the fresh gland and the appearance of fluid-like vacuoles between the free borders of the cells. Andersson, however, extended his observations to the effect that the vacuoles appeared in the cells in from one-quarter hour to four hours after injection, wandered to the free border of the cells, and were expelled into the lumen of the follicle as little bubbles with a granular membrane. As he was unable to stain the contents of these fluid-like vacuoles by any method at his command, he termed them chromophobe secretion. They were the precursors of the vacuoles constantly found in the border of the colloid. After the expulsion of the chromophobe granules from the cell, small deeply staining granules appeared in the cytoplasm, increased in size, and wandered to the free border of the cell and were discharged into the lumen of the follicle. He termed these granules chromophil secretion because of their affinity for stains. After the discharge of these granules, the cell appeared shrunken and exhausted. He thus described a chromophobe followed by a chromophil phase of secretion. The chromophobe bubbles, after their discharge into the lumen of the follicle, burst and dissolved the chromophil granules which followed. The colloid was a mixture of the two, and its density varied directly with the amount of the chromophil secretion. The colloid then passed back into the lymphatics through small intercellular canals.

Hürthle [13] studied the thyroids of dogs after partial resection of the gland, bile retention caused by duct ligation, and stimulation of the glands with electrodes. He described the chief and colloid cells of Langendorff and the transition stages. The colloid cells were regarded as living cells, and probably returned to the state of chief cells. After

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11. Wyss, H.: Ueber die Bedeutung der Schilddrüse, Cor.-Bl. f. schweiz. Aerzte **19**:175, 1889.

12. Andersson, O. A.: Zur Kenntniss der Morphologie der Schilddrüse, Arch. f. Anat. u. Physiol., 1894, p. 177.

13. Hürthle, K.: Beiträge zur Kenntniss des Secretions Vorgangs in der Schilddrüse, Arch. f. d. ges. Physiol. **56**:1, 1894.

stimulation of the gland by the foregoing methods, the intracellular colloid of Biondi was increased because it was produced faster than it was excreted, and was therefore stored in the cell. Desquamation of epithelial cells was also noted, and was regarded as the usual form of cell death. The colloid was derived from preformed droplets in the cells after Biondi, and also from the change in the cell protoplasm after Langendorff. Hürthle considered the vacuoles of Wyss and Andersson to be artefacts due to shrinkage, and he could not find them in osmic fixed material.

Bozzi [14] partially resected the thyroids of dogs and, later, studied the gland with a variety of technics, chiefly Altmann's for mitochondria. He recognized chief and colloid cells with transition stages. The chief cells were the more numerous and contained many fuchsinophilic, colloid-like granules, of various shapes and sizes. The colloid cells were granular in the early stages, and homogeneous, hyaline-like, in the last stages. The colloid was normally formed from the granules in the chief cells, and not by the cell degeneration. It passed to the lymph vessels through spaces between flattened or cuboidal cells, and also through degenerated areas in the follicle wall.

Schmid [15] studied the thyroids of various animals after partial resection and pilocarpinization of the animals. Just before the injection, one thyroid was carefully excised and fixed in osmic acid for control. In from one-half hour to four hours after the injection, the animal was killed and the other thyroid was fixed in the same fluid. On microscopic examination, no difference could be found between the control and the pilocarpinized gland. He rejected Andersson's results, and concluded that the thyroid is not affected by pilocarpin. The so-called vacuoles are artefacts due to poor fixation. Colloid droplets of Hürthle are too rare to be regarded as the ordinary secretion antecedent. The secretion of the thyroid arises through the change of the chief cells to colloid cells of Langendorff, and the discharge of their contents into the follicle. The colloid mass is retained secretion. It is discharged into the lymph vessel through gaps caused by a dissolution of the follicle wall. No intercellular canals exist.

Galeotti [16] studied the thyroid of turtles after the injection of various substances (urea, creatin, bile, gallic acid, xanthin, urine and putrefactive substances). He stained the secretion with acid fuchsin and methyl green and described two types of secretion antecedents in the

14. Bozzi, E.: Untersuchungen über die Schilddrüse, Beitr. z. path. Anat. u. z. allg. Path. **18**:125, 1895.

15. Schmid, E.: Die Secretionsvorgang in der Schilddrüse, Arch. f. mikr. Anat. **47**:181, 1896.

16. Galeotti, G.: Beitrag zur Kentnniss der Sekretionserscheinungen in den Epithelzellen der Schilddrüse, Arch. f. mikr. Anat. **48**:305, 1897.

cell: fuchsinophil granules of nuclear origin, and hyaline droplets of cytoplasmic origin staining with methyl green. There were no transitions between the two. Both were cast into the follicles, and the two varied independently of one another with the substances injected. The colloid cells of Langendorff were relatively rare, and were regarded as degenerating cells entering into the formation of the colloid.

Lobenhoffer [17] studied eighty normal and pathologic human thyroids after fixation in formaldehyd solution (formol) and Müller's fluid and stained with anilin acid fuchsin and picric acid. He described intracellular fuchsinophilic granules which were discharged into the follicles, quickly lost their identity, and entered into the composition of the colloid. They were scanty in the normal thyroid, absent in the malignant struma, markedly increased in colloid goiter and in the small alveolar large cell struma (fetal adenoma?). In Basedow's disease, they did not vary from the normal. He therefore concluded that in Basedow's disease there occurs a secretion anomaly in the form of an as yet unknown cell product, or a condition which allowed a rapid mixing and transportation of the secretion.

Ferguson [18] in studying the thyroid of elasmobranch fishes noted that the bases of many of the epithelial cells were rodded and granular, and suggested that the secretion was discharged directly from the base of the cell into the vacular channels. The colloid was regarded as stored secretion, and was stagnated albuminous material, the production of which was dependent on the rate of flow of the fluid from which it was formed. Its amount was no index of activity of the epithelial cells.

In 1911, Schultze,[19] in studying the relation between secretion granules and mitochondria in gland cells, included the thyroid in the group. He described the thyroid cells as containing a rich filar structure of mitochondria. Embedded in the filaments, he found dense granules, and concluded that the granules described by Lobenhoffer arose from the mitochondria. Almost simultaneously, Mawas [20] reported studies on the thyroid of rabbits in which the mitochondria were described as short rods and granules filling the protoplasm of the cells, except for a narrow zone around the nucleus. He found that all the cells of a follicle contained about the same amount of mitochondria, but that there was considerable variation in the nuclei, some being

17. Lobenhoffer: Beiträge zur Lehre der Sekretion in der struma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **20**:650, 1909.

18. Ferguson, J. S.: The Anatomy of the Thyroid Gland of Elasmobranchs, Am. J. Anat. **11**:151, 1911.

19. Schultze, O.: Ueber die Genese der Granula in den Drüsenzellen, Anat. Anz. **38**:257, 1911.

20. Mawas, J.: Sur la structure du protoplasma des cellules épithéliales du corps thyroïde de quelques mammifères, Bibliographie Anatomique **21**:256, 1910-1911.

vesicular and others staining deeply. He found no evidence of granules or droplets in the cell, and he regarded the changes in the nuclei as the only secretory manifestations of the cells which were visible. He consequently concluded that the cells secreted a substance slowly and continuously without apparent cycles and without the formation of granules. This secretion was not the colloid but some unknown substance, since the interstitial cells appeared active and did not secrete colloid into the vesicles.

Bensley,[21] in 1914, studied the thyroid gland of the opossum, both in the normal condition and in animals in which hyperplasia had been produced by a laboratory diet rich in meat and eggs. In the normal gland, he described ovoid interstitial cells filled with eosinophilic granules as of frequent occurrence. In the follicle cells, large crystals were found. These crystals gave strongly positive Millon's and xanthoproteic reactions, and disappeared as the gland became hyperplastic.

In the hyperplastic glands, the mitochondria were increased in number and size, and a new secretion antecedent appeared in the form of minute granules along the free border of the cell. These granules were best fixed in formaldehyd Zenker solution, and stained with neutral gentian or Mallory's phosphotungstic hematoxylin. Administration of iodin to these animals with hyperactive thyroids caused the reversion of the gland to the normal type, the disappearance of the granules, and the appearance of droplets of colloid deep in the cells.

The demonstration of mitochondria in the thyroid epithelial cells by Schultze and Mawas made necessary a reexamination of all previous work on secretion antecedents in the thyroid. This, Bensley [8] did in 1916, and his conclusions, based on his extensive researches on the cytology of gland cells, demand careful consideration. He concluded that the fuchsinophilic granules of Galeotti, Lobenhoffer and others were, in part at least, mitochondria rather imperfectly preserved. He stated, however, that nonmitochondrial fuchsinophilic granules did occur in hyperplastic glands. The colloid cells of Langendorff were cells in the last stages of cytomorphosis. He concluded that "the only secretory antecedents thus far demonstrated in the thyroid epithelial cells, which may be considered to be normal products, are the colloid globules of Biondi and Hürthle, to which also belong the chromophil granules of Andersson, and the so-called chromophobe secretion of Andersson." He had previously demonstrated [21] that, by diet, he could produce thyroid hyperplasia in the opossum and, by the administration of iodin, cause involution of the hyperplastic gland. The involution was accompanied by a slow accumulation of colloid droplets in the epithelial cells. The colloid droplets were ultimately discharged into the newly formed

21. Bensley, R. R.: The Thyroid Gland of the Opossum, Anat. Record 8:431, 1914.

lumen of the follicle, but the process was a very slow one. It was therefore concluded that the secretion of the colloid into the follicles is an accessory and not the chief function of the epithelial cells. The clear vacuoles found in the intrafollicular colloid were regarded as artefacts due to shrinkage.

Bensley had previously noted vacuoles in the basal zone of epithelial cells of thyroids of various animals. By means of an original technic (fixation in formaldehyd Zenker and staining with brazilin and Wasserblau), he was able to stain the contents of these vacuoles a sky blue on a pink to lilac background of protoplasm containing red mitochondrial filaments; the vacuoles occurred in the outer pole of the cell and were seen in the apical zone only in cases in which the cell was so loaded with secretion that it was comparable to a parotid gland cell filled with xymogen granules. Bensley concluded that these vacuoles represented the true secretion of the gland, and that the substance passes directly from the base of the cell to the vascular channels and does not enter the follicle at all. He thus ascribes to the thyroid epithelial cells a true reversal of polarity in accordance with their endocrine function. As corroborative evidence of this reversal of polarity, he states that in the thyroid cells the intracellular fat droplets are deposited in the antisecretory apical zone next to the colloid, while in exocrine glands they are always in the basal zone (antisecretory). The colloid represents an excess of secretion which is condensed in the cell and stored in the follicle, and its amount and density are per se no measure of the activity of the gland at the moment of observation, though they may offer valuable evidence of the capacity of the thyroid cell for storage. The colloid may be the product of a storage phase which preceded the examination of the gland by a considerable period of time.

Following Bensley's observations of the increase of mitochondria in the hyperactive glands of the opossum, Goetsch [1] studied the mitochondria in a series of pathologic human thyroids, with the results noted in the beginning of this article. In general, they were increased in toxic adenoma and in exophthalmic goiter, and decreased in the nontoxic goiters. In a recent article, Goetsch [22] has described the mitochondria as increased in the interstitial cells in a condition of diffuse adenomatosis accompanied by symptoms of hyperthyroidism but with little or no increase in basal metabolism.

Cowdry,[23] in studying the reticular material (Golgi net) of the thyroid cells of the guinea-pig, has noted that it is not always restricted

22. Goetsch, E.: Studies on Disorders of the Thyroid Gland, Hypersensitiveness Test, Etc., Endocrinology **4**:389, 1920.

23. Cowdry, E. V.: The Reticular Material as an Indication of Physiologic Reversal in Secretory Polarity in the Thyroid Cells of the Guinea-Pig, Am. J. Anat. **30**:25 (Jan.) 1922.

to the zone of cytoplasm between the nucleus and the follicular cavity, but is found in about one cell in every 500 in the opposite pole near the peripheral blood vessels. In the pancreas and other exocrine glands, the reticular material is invariably located between the nucleus and the discharging zone of the cell. Cowdry concludes that this presence of the reticular material in the basal zone, together with other evidence at hand, indicates the existence of a reversal in physiologic polarity whereby the secretion of the thyroid is discharged directly into the circulation, instead of being first stored within the follicles. That this is a true reversal of polarity is evidenced by the fact that the follicle space represents the ancestral duct or lumen of the gland. This is proved by the usual position of the reticular substance, and by the author's previous observation [24] that, in the dogfish, the cells bordering the follicles are uniformly flagellated.

It is thus seen that there is a wide divergence of opinion among investigators as to the normal mode of secretion in the thyroid. In this investigation I have endeavored to determine the normal mode of secretion in the gland, and then to study the pathologic glands as a departure from the normal.

MATERIALS AND METHODS

The material consists of portions of sixty-five pathologic human thyroids which were fixed soon after their removal at operation. In Cases 18 and 19, only small portions of tissue removed at operation for ligation were available, and consequently the data in these two cases is not very reliable. In all the other cases, at least four and often ten or more blocks of tissue from various portions of the gland were cut and studied for mitochondria and secretion antecedents. In addition, thyroids of normal cats, dogs, rabbits, rats and guinea-pigs were studied.

A number of pieces of all the glands studied were fixed in the formaldehyd bichromate of Regaud [25] and formaldehyd Zenker mixtures of Bensley,[26] and in Zenker's fluid. At various times, portions of individual glands were fixed in a wide variety of fluids in an attempt to differentiate certain granules and vacuoles, which will be mentioned later.

The tissues were, as a routine, washed in running water over night, dehydrated in graded alcohols, cleared in xylene, and embedded in paraffin (56-58 degrees). Secretions were cut at 4 microns, fixed to the

24. Cowdry, E. V.: Flagellated Thyroid Cells in the Dog-Fish (Mustelus Canis), Anat. Record **22**:289, 1921.

25. Regaud, C.: Etudes sur la structure des tubes séminifères, Arch d'anat. micro. **11**:291, 1910.

26. Bensley, R. R.: Studies on the Pancreas of the Guinea-Pig, Am. J. Anat. **12**:297, 1911-1912.

slide by the water-albumin method and stained by various technics. For the demonstration of mitochondria, Bensley's anilin acid fuchsin and methyl green, Altmann's anilin acid fuchsin and picric acid, Regaud's iron hematoxylin, and Benda's alizarin gentian violet methods were used. For the study of secretion granules, Mallory's phosphotungstic acid hematoxylin, Bensley's neutral gentian, Bensley's brazilin Wasserblau, and Ehrlich-Biondi's acid fuchsin methyl green-orange G methods were used. Intracellular fat was studied in teased fresh tissue and frozen sections of formaldehyd fixed tissue stained with sudan III and Herxheimer's alkaline scarlet R. Small blocks of tissue were fixed in 2 per cent. osmic acid for periods varying from twenty-four hours to four weeks, and studied for fat and the reticular apparatus.

In order to confirm as far as possible the observations on fixed tissue, bits of a number of thyroids were teased out in physiologic sodium chlorid solution and studied, unstained and after treatment with various supravital dyes and a variety of chemical reagents. The method found to be most satisfactory for the study of mitochondria and chromophobe secretion was fixation in formaldehyd bichromate by Regaud's [25] method IV B and staining with the anilin acid fuchsin methyl green of Bensley as recommended by Cowdry.[27] Unless otherwise stated, the descriptions that follow are all based on material fixed and stained by this method. The routine method adopted for the demonstration of the chromophil secretion granules was fixation in Bensley's formaldehyd Zenker mixture and staining with Mallory's phosphotungstic hematoxylin.

THE NORMAL THYROID

In this study, the various pathologic conditions of the gland have been considered as departures from the normal, and it will first be necessary to describe in detail the histology and cytology of the normal thyroid. On account of the wide variations in functional activity and the corresponding anatomic variations as noted by Marine, I have had considerable difficulty in arriving at a definite conception of what may be considered the normal thyroid of the adult human. This difficulty has been increased by the fact that, for the study of the cytology, it is necessary to obtain the tissue soon after death, and in the case of the human this has not been possible. However, the difficulty has in part been overcome by the study of portions of human glands removed at operation for adenomas. It is to be pointed out that these are not absolutely normal, as it has been noted by Marine that adenomas are frequently accompanied by a generalized hyperplasia of the gland. However, from a study of such glands and comparing them with the

27. Cowdry, E. V.: The Mitochondrial Constituents of Protoplasm, Contribution to Embryology, No. 25, Carnegie Institute Publication 8:38, 1918.

histology of the normal human gland removed at necropsy and the cytology with that of the thyroids of normal dogs, cats, rabbits, guinea-pigs and rats, it has been possible to arrive at a standard which is used as a base-line for departure in the study of the various pathologic conditions.

The normal thyroid consists of a mass of closed noncommunicating follicles, which are filled with colloid and lined by a single layer of epithelial cells. The gland is surrounded by a rather thin capsule of fibrous and areolar connective tissue. Trabeculae arising from the inner surface of the capsule extend into the gland, giving it a faintly lobulated appearance and forming its stroma or supporting framework in which the follicles rest. The trabeculae consist of rather delicate fibrous and areolar connective tissue, and carry the numerous blood and lymph vessels and nerves of the gland. The stroma is increased in amount around the larger blood vessels, and more delicate processes extend in all directions to support the smaller vessels and ultimate capillaries, which form a rather dense network around the individual follicles. Thus is formed a delicate connective tissue reticulum which extends throughout the gland and surrounds and supports the follicles. The stroma of the normal gland is scanty in amount and delicate in structure. In the angular spaces between the follicles, the stroma is areolar in character, and here are found a variable number of interstitial glandular cells, fat and lymphoid cells. Occasional lymph nodes are found in the normal gland. Simmonds [28] has studied the distribution of lymphoid tissue in a series of supposedly normal thyroids from necropsies of patients dying from various conditions.

The follicles, which are the unit of structure of the gland, are roughly spherical or ovoid in shape, except near the periphery of the gland where they tend to be flattened with their long axes parallel with the capsule. In size, they vary considerably in different glands and in the same gland. They may roughly be divided into two types: the adult and the young follicles. The adult follicles, which are the predominating type of the adult human gland, average from about 0.3 to 0.5 mm. in diameter. In the angular spaces between the adult follicles are found a variable number of young follicles averaging from 0.025 to 0.05 mm. in diameter, and all transitions between the two types can be found in the same gland. In young persons, the follicles tend to be smaller and more uniform in size. In old persons the thyroid contains many large, dilated follicles, quite distended with the colloid that fills them. Not uncommonly, however, the regular contour of one of these dilated follicles is broken by a projection from the wall; either as a single fold

28. Simmonds, M.: Ueber lymphatische Herde in der Schilddrüse, Virchows Arch. f. path. Anat. **211**:73, 1913.

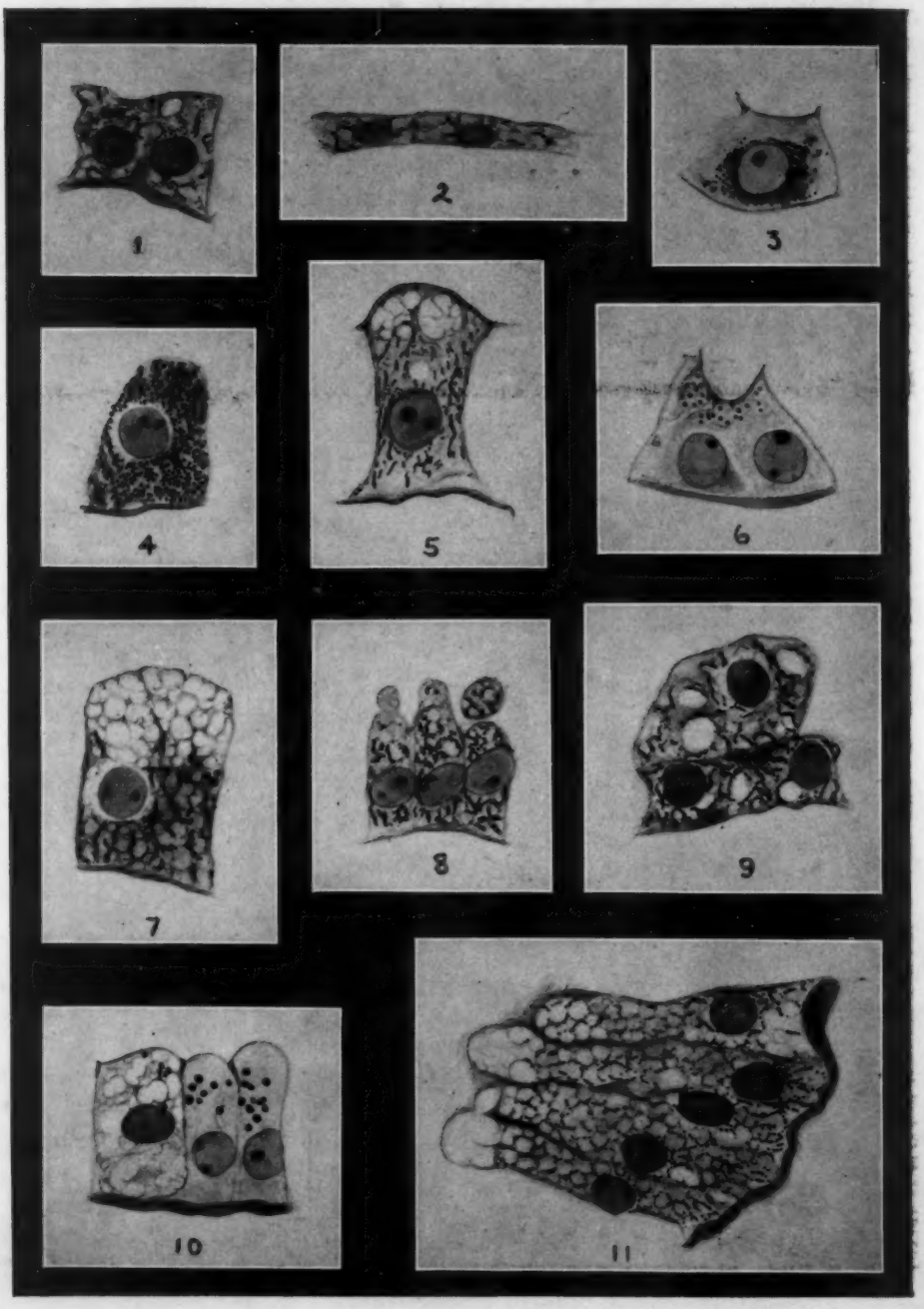
of stroma covered on the two sides by epithelial cells, or as an irregular mass of cells extending for a variable distance along one side of the follicle. The thin twiglike projections may be interpreted either as outgrowths from the wall which tend to subdivide the follicles, or as the remainder of the walls of two follicles which have fused by the partial dissolution of their adjacent walls. The cellular projections are generally considered to be localized areas of regeneration.

The epithelial cells that line the follicles are arranged in a single layer and rest on the connective tissue reticulum that surrounds the follicle and forms the stroma of the gland. It is commonly stated that the cells come into direct relationship with the blood and lymph vessels. Whether or not this is ever true, I am unable to state with certainty; but a study of sections stained by Van Gieson's and Mallory's methods for the demonstration of connective tissue leads me to believe that the follicles are everywhere surrounded by a layer of connective tissue which, however, is for the most part extremely thin and delicate.

In shape, the follicular cells (Figs. 1 and 2) vary from extremely flattened endothelial-like cells with projecting nuclei to cuboidal or low columnar cells from 8 to 10 microns in height. This wide variation in shape is apparently partly dependent on the mechanical conditions under which the cells exist, as the large dilated follicles distended with dense colloid are lined by the flattened cells, and the smaller follicles containing thin colloid are lined by the higher cuboidal or pyramidal cells. A second factor is the age of the cell, as the younger cells characteristic of the regenerating areas noted above are low columnar cells, though they may be present in the wall of a follicle that elsewhere is lined by flattened cells. The mature follicles of the normal gland are lined by rather dormant looking low cuboidal cells from 5 to 7 microns in height. As a rule, the height of the cells varies inversely with the size of the follicle and the density of the colloid.

In the flattened cell, the nucleus causes a central projection into the lumen of the follicle, and the protoplasm tapers out to a thin edge on all sides. In the cuboidal cell, the apex is domelike, and this, on section, gives the colloid a serrated edge, and therefore the colloid appears actually to dip into the spaces between adjacent cells. Lewis [2] has called attention to the intercellular cement substance which in sections, through the apexes and perpendicular to the long axes of the cells, gives a mosaic-like appearance to the area. This condition is best seen in the high columnar cells of exophthalmic goiter, but it is also true of the normal gland. In sections cut parallel to the long axes of the cells, there is a small deeply staining triangular area separating the adjacent borders of the cells. By studying cells cut in various planes, it is seen that this dense substance forms a ring around the apex of each cell. In my experience, it has always given the same staining reactions

PLATE 1



Explanation of Plate 1

Figures 1 to 12 are camera lucida drawings made by Miss Piotti; magnification × 970. Figures 12 to 16 and 21 and 22 are photomicrographs ocular 6; objective, 8 mm. Figures 17 to 20 are ocular 4; objective, 1.9 mm.

All the figures, except Figures 6, 10, 18, 19, 20 and 22 are from tissue fixed by Regaud's method 4 B, stained by Bensley's acid fuchsin methyl green technic; Figures 6, 10, 19 and 20 are from tissue fixed in Bensley's formaldehyd Zenker, stained with Mallory's phosphotungstic acid hemotoxylin; Figures 18 and 22 are from material fixed in Bensley's acetic osmic bichromate mixture. All sections were cut at 4 microns.

Fig. 1.—Cells from follicle of normal human gland; mitochondria; one secretion vacuole.

Fig. 2.—Cells from same follicle as shown in Figure 1; mitochondria.

Fig. 3 (Case 1).—Cells from a fetal adenoma; varying amounts of mitochondria but no secretion antecedents.

Fig. 4 (Case 1).—Same as Figure 3.

Fig. 5.—Fetal adenoma columnar cell containing chromophobe vacuoles in the apical form.

Fig. 6.—Chromophil granules in section of wall of small follicle in fetal adenoma cell.

Fig. 7.—Two adjacent cells from exophthalmic goiter glands; three chromophil granules in cytoplasm of cell on right; nucleus of cell not included in section.

Fig. 8.—Three cells from follicle of exophthalmic goiter gland shedding their apexes into the follicle.

Fig. 9.—Large interstitial cell from exophthalmic goiter gland lying in the stroma beneath two follicle cells.

Fig. 10 (Case 25).—Three cells showing the maximum amount of chromophil secretion granules seen in any gland; mitochondria not stained; numerous chromophobe vacuoles throughout cell on left.

Fig. 11.—Group of very tall columnar cells with chromophobe vacuoles in the apexes and in the base of cell on right.

as the dense colloid, and it impresses one as being colloid which is forced down between the cells by pressure within the follicles. However, its presence in follicles containing little or no stainable colloid suggests that it is not colloid, but is intercellular cement substance, as suggested by Lewis. In thin sections, I have not been able to detect any particular thickening of the cell membrane along the free border which some observers have described as cuticle-like. The appearance, I believe, is due to adherent colloid or to a section through the convex surface.

The cells of the follicle each contain a single round or oval nucleus which is relatively quite large (from 4 to 6 microns). The larger nuclei found in the higher cuboidal cells are ovoid, with their long axis parallel to that of the cell. In structure, they are vesicular, with a thin chromatin network and from two to four nucleoli. In the flattened cells, the nuclei are smaller, flattened against the base of the cell, stain more diffusely and deeply, and their nucleoli are not so prominent. In tissue fixed in formaldehyd bichromate of Regaud, there is a wide variation in the staining qualities of the nuclei of cells of the same type in the same follicle, some staining deeply and diffusely and others being vesicular. Mawas [20] has stated that these changes are indicative of the functional state of the cells, and are the only criteria of functional activity of the follicular cells. However, he does not state which are the active and which the resting cells. But Regaud's fluid is a very poor fixative for nuclei, and I believe that these variations in the staining of the nuclei are due to poor fixation. In tissue fixed in Zenker's fluid, which is a good nuclear fixative, the variations are not seen and the nuclei are quite as uniform as in other glandular cells. Exceptions, of course, are the pyknotic nuclei of the colloid cells which will be mentioned later.

The cytoplasm of the follicular cells stains lightly with green, and contains a moderate number of fuchsinophilic granules and occasionally a clear vacuole (Fig. 1). The granules, on the basis of studies on hyperplastic human glands and normal glands of the various laboratory animals, I have been able to divide into mitochondria and secretion granules.

The mitochondria are similar in solubility and staining characteristics to those found in all other living cells, and their general characteristics need not be considered here, as they have been dealt with fully by Cowdry [27] and, more recently, by Key.[29] In the follicle cells, they are present as small granules and rodlike masses and filaments scattered irregularly through the protoplasm. The rods and filaments vary con-

29. Key, J. A.: Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. **28**:511 (Nov.) 1921.

siderably in length, and are usually more or less irregularly curved, but remain delicate in structure and fairly constant in diameter. No granular inclusions, such as those described by Schultze,[19] were demonstrable. In the low cuboidal cells of the normal gland there is no appearance of polarity. The mitochondria are present in the basal and apical zones and on either side of the nucleus, and are not concentrated in any particular region of the cell. In the flattened cells, they exhibit a slight tendency to be concentrated in the thicker zone of cytoplasm around the nucleus, but the minute granules are found far out in the thinned out cell body. In number and size, they vary with the size of the cell containing them. In the flattened cells, as is to be expected because there is less cytoplasm, they are smaller and fewer in number. In the cuboidal cell of the normal gland, they are present in moderate numbers (from ten to twenty small granules or rods per cell is a fair average for tissue cut at 4 microns). However, numbers mean little on account of the wide variation in length of the filaments. In the larger cells of the smaller vesicles, the mitochondria are slightly larger and more numerous but do not crowd the cytoplasm. That is, they are absolutely but not relatively increased. In the lower columnar cells of regenerating areas, the mitochondria are both absolutely and relatively increased, and often crowd all the available cytoplasm.

The secretion granules (Figs. 6, 7, 10, 19 and 20) are spherical in shape, and vary in size from minute granules to spherules from 1.5 to 2 microns in diameter. In the normal human thyroids that I have examined, these granules have been very rare, only one or two as a rule being found in an occasional cell after considerable search through a section. When present in a cuboidal cell, they usually lie in the apical zone next to the free border of the cell. In the flattened cells, they lie along the side of the nucleus. They are present in the thyroids of rabbits, guinea-pigs and dogs in considerable numbers, and were found to be very numerous in the thyroids of a number of cats that were studied. That is to say, the average cell of the cat's thyroid contained from eight to twelve large spherical granules. In certain of the pathologic human thyroids studied, these granules were present in considerable numbers. By the study of these pathologic human glands and cats' thyroids, it has been possible to differentiate these granules from the minute mitochondria.

The secretion granules are strongly fuchsinophilic, and in tissues stained by Cowdry's[27] method cannot be differentiated from the mitochondria except by their uniformly spherical shape; the mitochondria are usually rod shaped. However, if the differentiation with the methyl green is carried too far, most of the mitochondria, if not all, are decolorized, and the secretion granules remain red or are deeply stained with the green. It was in this way that these granules

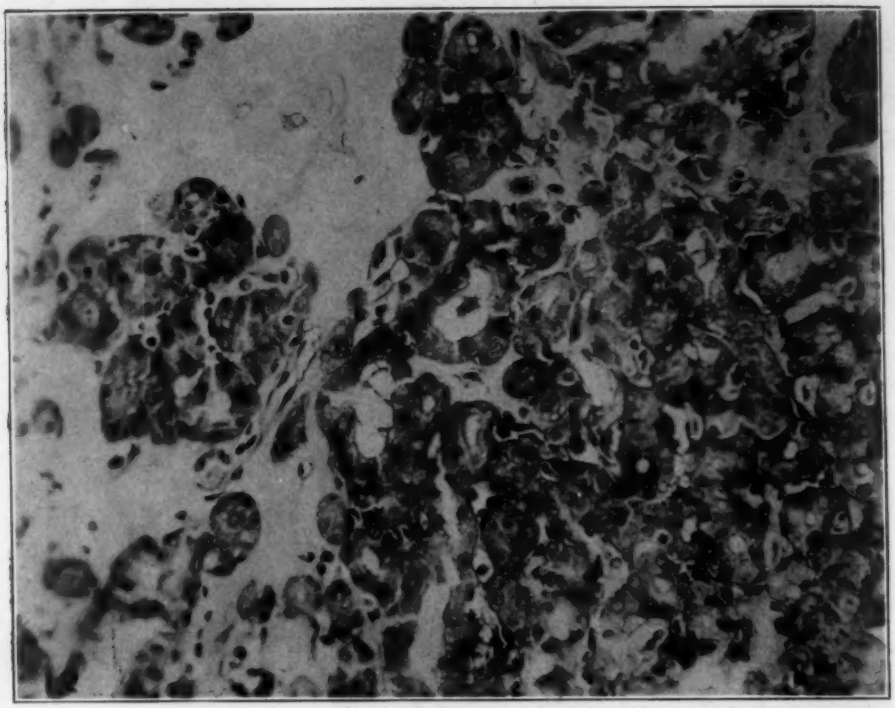


Fig. 12 (Case 1).—Moderately active fetal adenoma.

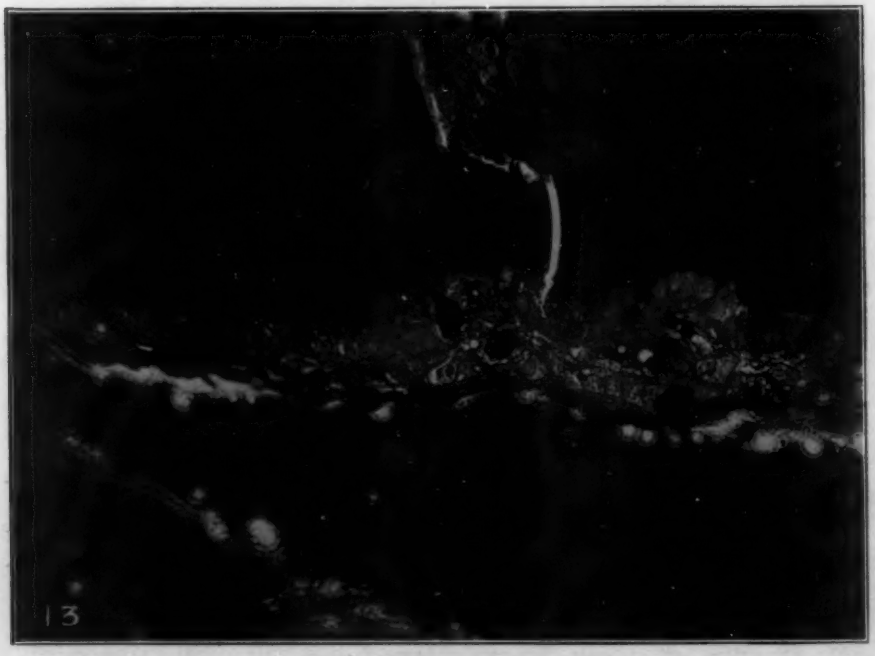


Fig. 13.—Simple, nontoxic adenoma; small regenerated area in wall of dilated follicle.

were first brought to my attention, since the mitochondria have never in my experience taken the methyl green stain. Also, if the treatment with potassium permanganate be unduly prolonged (ten minutes), the mitochondria lose their staining capacity, while the secretion granules can be stained with the acid fuchsin.

They are also preserved by all the mitochondrial fixatives with which I am familiar, and take the same stain as do the mitochondria. They differ from the mitochondria, however, in that they are somewhat more readily fixed and stained than are the mitochondria themselves.

In tissue fixed for forty-eight hours in 2 per cent. osmic acid, the secretion granules are blackened and resemble fat droplets, while, in order to blacken the mitochondria, the more prolonged fixation (four weeks [30]) is necessary. Likewise, when the tissue is fixed in Bensley's acetic osmic bichromate mixture, the secretion granules are dark brown to black and resemble lipoid or fat. That they are not fat droplets, however, is evident from the fact that they are well fixed in formaldehyd bichromate or formaldehyd Zenker mixture, and are not dissolved by the alcohols used in dehydrating the tissue for embedding. They are more resistant to acetic acid than are the mitochondria, and it is possible to stain them in tissues fixed in a mixture of twenty parts of formaldehyd, ten parts of acetic acid, seventy parts of 3 per cent. bichromate. They are also preserved in Zenker's fluid containing 5 per cent. acetic acid and in the various mixtures of formaldehyd sublimate and alcohol which do not preserve the mitochondria. In tissue fixed in 10 per cent. formaldehyd, they are preserved, and can be seen in the frozen sections, but disappear during the process of dehydration unless the tissue is first mordanted in bichromate.

The best results are obtained after fixation in Bensley's formaldehyd Zenker mixture. In my hands, formaldehyd Zenker mixture has always been a very poor mitochondrial fixative but excellent for secretion granules.

If well fixed and numerous, the secretion granules can be stained by a wide variety of methods. In my hands, the most consistent results have been obtained by staining from four to eight hours in the phosphotungstic hematoxylin of Mallory. By this method, the granules are stained dark brown to blue black on a reddish brown background. If formaldehyd bichromate material is used, some of the mitochondria may be stained a pale blue, especially after from twelve to twenty-four hours.

The secretion granules are stained red with acid fuchsin; blue black with iron hematoxylin; violet with gentian violet, crystal violet or neutral gentian; red with safranin or Bensley's brazilin Wasserblau

30. Jordan, H. E.: Mitochondria and Golgi Apparatus of the Giant-Cells of Red Bone-Marrow, Am. J. Anat. **29**:117 (May) 1921.

method; blue with the various methylene blues or azures, and the green with methyl green. It is thus seen that they can be stained by a wide variety of stains which do not stain the mitochondria. It has not, however, been found possible to stain them and the mitochondria differentially in the same preparation. Bensley's combination of his acid fuchsin and neutral gentian methods, which gives excellent preparations for the pancreas, was not very successful when applied to the thyroid.

In addition to the granules described above, the normal acinous cells contain another secretion antecedent in the form of small clear vacuoles (Figs. 1, 5, 7, 8, 9, 10, 11, 17, 18 and 22). These vacuoles are best seen in tissue fixed by Regaud's [20] formaldehyd bichromate method IV B, but are well seen in tissue fixed in Bensley's [26] acetic osmic bichromate mixture. In formaldehyd Zenker material, those in the depths of the cell are usually preserved while those near the apex are destroyed. In Zenker's fluid, practically all of them are destroyed. Their preservation apparently depends on the thorough fixation of the surrounding cytoplasm so that the form of the vacuoles is preserved, though they contain no stainable contents. After formaldehyd Zenker fixation, many of them contain a thin coagulum which can be stained light blue by Bensley's [8] brazilin Wasserblau. But they are easily seen as clear, apparently empty, vacuoles on a green background in tissue fixed in formaldehyd bichromate and stained with Bensley's acid fuchsin methyl green, and it is questionable whether or not the thin coagulum seen in formaldehyd Zenker material is not due to imperfect fixation of the surrounding cytoplasm. These vacuoles are, I believe, identical with the chromophobe secretion of Andersson.[12] That they are not true vacuoles left by the absorption of fat is evidenced by the fact that they can be seen as clear spaces in tissue fixed for four weeks in 2 per cent. osmic acid. With the exception of Andersson, observers have either not seen them at all or have regarded them as artefacts. Reasons will be given later which indicate that they contain the active secretion of the thyroid gland.

In the normal thyroid of man, these chromophobe vacuoles are not numerous. They are found as one to three or four small, clear, spherical or oval vacuoles in only an occasional cell. In size, they vary from very minute to large vacuoles from 2 to 3 microns in diameter. In the flattened cells, they lie along the side of the nucleus, and in the cuboidal or low columnar cells they are usually in the apical zone near the colloid, but may be seen in the depths of the cell body or even in the basal zone between the nucleus and the basement membrane.

The reticular apparatus or intracellular network of Golgi has recently been described by Cowdry [23] in the cells of the thyroid of the guinea-pig. In the human thyroid, the reticular apparatus can be demonstrated in tissue fixed for four weeks in 2 per cent. osmic acid. In thin sections

Fig. 14 (Case 14).—Exophthalmic goiter.

Fig. 15 (Case 4).—Exophthalmic goiter.

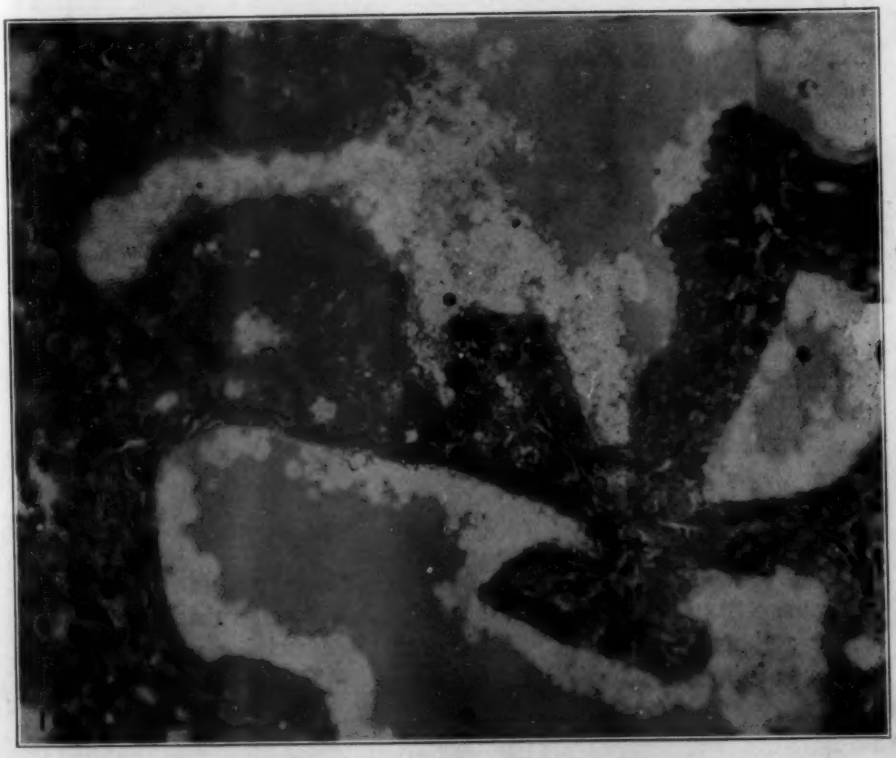


Fig. 16 (Case 32).—Exophthalmic goiter.

of such thyroid tissue mounted without other staining, the reticular apparatus is found to be blackened by the osmic acid while the remainder of the cytoplasm is brown. It usually appears as a black skein or irregular net which lies quite close to and partly encircles the nucleus. In amount, it varies considerably in different cells of the same acinus. In position, as a rule, it lies in the cytoplasm between the nucleus and the lumen of the follicle. However, as was pointed out by Cowdry in the guinea-pig, the reticular material in the human thyroid is not constant in position but is occasionally seen lying lateral to the nucleus or even in the basal zone of the cytoplasm between the nucleus and the basement membrane.

Intracellular droplets of colloid are rarely seen in the cells of the normal human gland. When found, they occur as an irregular round or oval droplet lying in the cytoplasm, usually near the nucleus. The droplets vary in size from small droplets to large ones almost as large as the nucleus of the cell. Since the intracellular colloid stains similarly to the secretion granules, it is difficult to differentiate the small droplets of colloid from these granules if the granules are fixed. Likewise, the large droplets are apt to be confused with deep staining nuclei. This is particularly true of formaldehyd bichromate material in which many of the nuclei stain diffusely and resemble colloid droplets.

The position of the intracellular fat droplets in the thyroid assumes importance since Bensley [8] in his studies on the thyroid of the opossum has described the intracellular fat droplets as being present in the apical zone of the cells. As is well known, in exocrine glands such as the pancreas, the secretory cells normally contain a few small fat droplets, which are located in the basal zone of the cell, and as a rule are quite close to the basement membrane. This reversal of position of the fat in the thyroid, Bensley offers as corroborative evidence in support of his theory of the reversal of polarity in the thyroid. After studying a number of pathologic human thyroids and the normal glands of laboratory animals by means of fixation for various periods in osmic acid and staining fresh and formaldehyd fixed tissue with scarlet R and sudan III, I have not been able to decide definitely as to the location of the intracellular fat. This is because the chromophil granules which have been mentioned are blackened by osmic acid, and stain more or less deeply with the fat stains.

It can, however, be stated that in the glands that I have examined for fat there are some small globules in the basal zone of many cells which give the reactions for fat mentioned above. In the apical zone of the same cells, there are to be seen granules or globules that are usually larger and more numerous and give the same staining reactions. In sections of the same glands fixed in formaldehyd Zenker or formaldehyd bichromate, there are no small globules in the base of the cells but

secretion granules are present in the apical zone. So, at present, one must admit two possibilities: either the intracellular fat is present in both poles of the cell, or it is present in small amount in the basal zone only and the apical zone contains secretion antecedents that give a similar reaction and confuse the picture. In the much flattened cells lining many of the dilated follicles, no polarity can be made out and the fat, if present, lies along the side of the nucleus.

In addition to the normal acinous cells described, there are to be found a variable number of deeply staining cells, the so-called colloid cells of Langendorff. These cells are scattered irregularly through the gland lying between the normal cells lining the follicles. They are often more or less completely detached from the basement membrane. In form, they resemble the surrounding normal cells, being flattened or cuboidal as the case may be. It is to be noted, however, that they appear shrunken, being compressed laterally and having a concave rather than a convex free border. The nuclei are shrunken and pyknotic. The cytoplasm stains deeply with acid fuchsin and is usually homogenous, though in some cases it is filled with coarse fuchsinophilic granules. All transitions between these colloid cells and the normal cells can be found in the same gland. They are undoubtedly normal cells undergoing degeneration.

In the stroma of the gland, usually in the angular spaces, between three or more follicles are to be found a variable number of rather large ovoid cells, the interstitial cells or so-called embryonal cells of Wolffer. They are often from three to four times as large as the follicular cells, and their spherical nucleus is larger and more vesicular than that of the follicular cells. The mitochondria are quite abundant, and appear as small granules or short rods scattered throughout the cytoplasm. These cells are apparently actively engaged in the process of secretion as secretory antecedents in the form of chromophil granules, and chromophobe vacuoles similar to those in the follicle cells can be demonstrated in some of them. Cells similar to the interstitial cells are occasionally found in the walls of follicles, and all transitions between them and the normal follicular cells can be found. Furthermore, the interstitial cells are often seen to be engaged in the formation of new follicles. The evidence seems to indicate that these are not a different type of cell, but that because of their location in the stroma they are irregularly ovoid in shape and better nourished and more robust than the follicular cells. Possibly a large percentage of them are follicular cells that have wandered back into the surrounding stroma and become rejuvenated in the more favorable environment.

The colloid of the normal thyroid is usually homogeneous, and fills and distends the follicles. It is of moderate density, and stains deeply

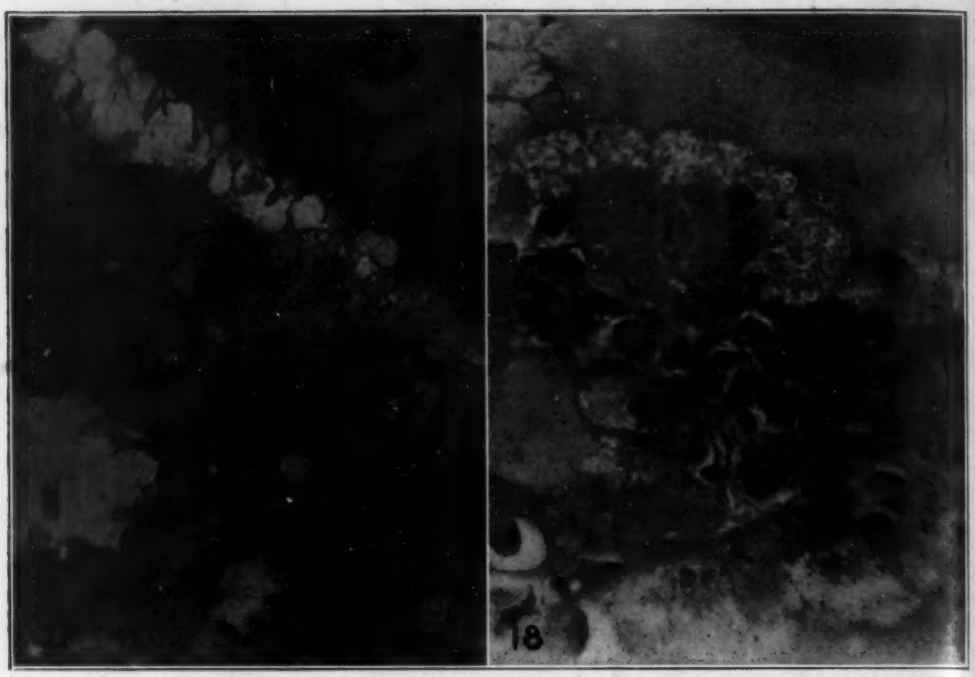


Fig. 17 (Case 12).—Exophthalmic goiter; chromophobe secretion.
Fig. 18. (Case 20).—Exophthalmic goiter; chromophobe secretion.

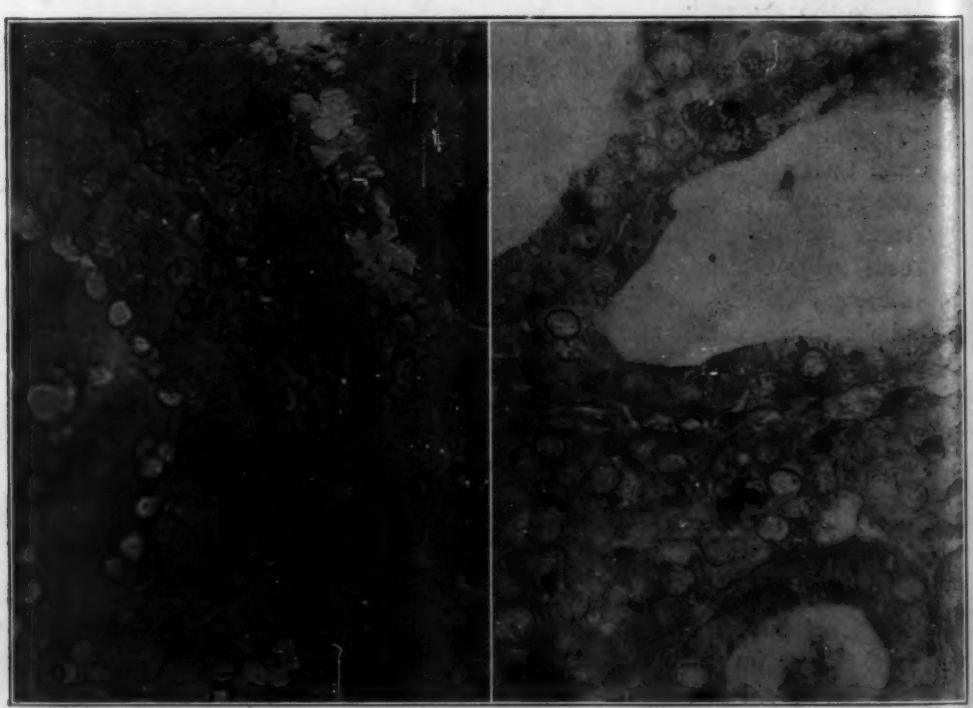


Fig. 19 (Case 25).—Exophthalmic goiter, chromophil secretion granules.
Fig. 20 (Case 14).—Exophthalmic goiter, chromophil secretion granules.

with acid fuchsin. In differentiating with methyl green, it is partly decolorized and tinted with green. The more dense the colloid, the more difficult it is to decolorize, and the dense colloid found in the atrophic follicles of normal glands remains deep red. The dense colloid is more common in the glands of older persons, and is contained in follicles which, as a rule, are lined by flattened or atrophic epithelium, with the exception of regenerating areas which may or may not be present. Occasionally, red blood cells, leukocytes and desquamated epithelial cells are present in the colloid of the normal gland. At times, the colloid may be granular, but as a rule it is homogeneous.

The colloid, unless it is shrunken during fixation or dehydration, is in direct contact with the surface of the lining cells, and fills the indentations between the domelike apexes of the higher cells. Very rarely, thin processes of what is apparently colloid can be seen extending between adjacent cells to the basement membrane. In the colloid, usually at the periphery in close relation to the cells, but occasionally in the interior of the mass, are seen a number of small, clear, vacuole-like areas which resemble minute air bubbles in the section. They vary in size and number in different follicles, and many follicles are entirely free from them, while an adjacent follicle may contain fifteen or twenty in a 4 micron section. In the normal gland, they are rarely over 20 microns in diameter. Occasionally, one of these vacuoles is seen to contain a thin coagulum which stains as does thin colloid. This is especially true of formaldehyd Zenker material. More rarely, a small droplet of colloid or one or more granules resembling the chromophil granules may be present in the interior of a vacuole. The line of demarcation between the vacuole and the surrounding colloid is clear cut, but no limiting membrane, such as was described by Andersson, can be identified. With the exception of Wyss [11] and Andersson,[12] observers have either disregarded these vacuoles or have considered them artefacts due to shrinkage. In shrinkage, the colloid mass contracts as a whole. The contraction is usually asymmetrical, the mass remaining adherent to one side of the follicle and pulling away from the opposite side. In both the attached and the free edge of the shrunken colloid, the small clear vacuoles may be present. Contrary to the descriptions of Hürthle [13] and others, these vacuoles can be definitely identified in tissue fixed in osmic acid or various osmic mixtures. They are, however, reduced in size and number and contain more coagulum when compared with formaldehyd bichromate material of the same gland. It is consequently believed that these vacuoles represent the chromophobe secretion of the cells described which is poured out into the follicles. It is difficult to determine whether or not the picture seen in sections is present in the normal gland, but I am inclined to think that it is an indication rather than an actual picture of conditions present in the

living gland. In fresh thyroid tissue teased out in salt solution and examined with a lowered condenser, one can occasionally see clear, spherical, fluid-like areas in the colloid of intact follicles, but they are rare and difficult to identify. It is probable, therefore, that the vacuoles in the follicles represent areas of increased fluidity in the colloid, which in fixation becomes more sharply separated from the more dense colloid. Thus, in a limited sense, they are artefacts, but they are not to be disregarded because they are indicative of definite areas of increased fluidity and, as will be shown later, are subject to wide variation coincident with alteration in the functional state of the gland. The decreased number of these vacuoles in tissue fixed in osmic acid, as compared with portions of the same gland fixed in formaldehyd bichromate or Zenker's fluid, is possibly due to the more rapid action of the latter fluids as well as their tendency to cause contraction of the colloid.

In the cells of the fresh tissue examined in salt solution, the mitochondria are seen as moderately refractile rods and granules distributed throughout the cytoplasm. The chromophil granules are more highly refractile than the mitochondria and more easily seen. They are rather coarse, spherical granules, and in the higher cells are located in the apical zone next to the colloid. The chromophobe secretion is not refractile, and is more difficult to identify. In tissues from the hyperactive glands, clear vacuole-like areas can be seen in the apexes of many cells, and these correspond to the chromophobe vacuoles present in the fixed tissue.

If the fresh gland tissue is stained with Janus green B (1:10,000) in physiologic sodium chlorid solution, the mitochondria and the chromophil granules are both stained green. They can be differentiated, however, by ringing the preparation with petrolatum and leaving it for some hours. The mitochondria disappear completely, but the secretion granules persist indefinitely and may or may not turn pink from the reduction of the dye to diethylsafranin. The secretion granules are also different in that they can be stained with neutral red, thionin, pyronin, azur I or II, and methylene blue, which do not stain the mitochondria.

Treated with 5 per cent. acetic acid, the mitochondria are dissolved immediately, and the secretion granules appear to swell and slowly lose their high refraction and are difficult to see after an hour or so. Treated with osmic acid, they are blackened and resemble fat droplets. They further resemble fat in that they are soluble in alcohol and can be stained with scarlet R or sudan III. On the other hand, they resemble proteins in that they are colored yellow by nitric acid (xanthoproteic) and give a faintly positive Adamkiewicz reaction and Millon's test.

Fig. 21 (Case 49).—Exophthalmic goiter; a follicle in which active shedding of the apexes of the cells is going on.

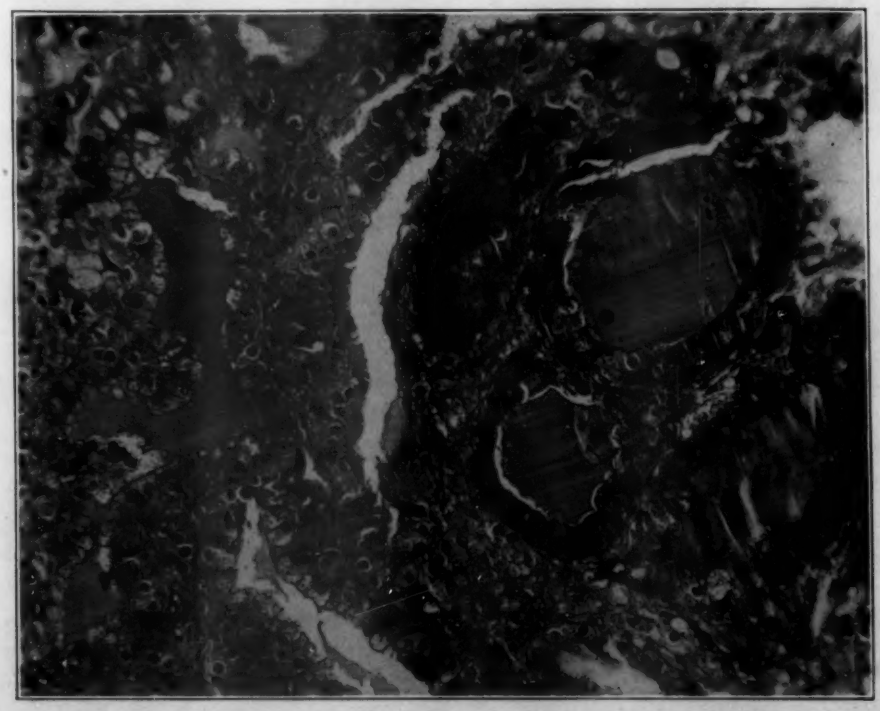


Fig. 22 (Case 20).—Exophthalmic goiter; small islet of fuchsinophilic cells.

PATHOLOGIC THYROID GLANDS

The sixty-four specimens studied included fifteen simple adenomas, thirteen fetal adenomas, one colloid goiter, thirty-three exophthalmic goiters and two malignant tumors. All were studied cytologically, and an attempt was made to determine in what respect and to what extent each specimen varied from the normal thyroid. In Tables 1, 2 and 3, the increase or decrease as compared to the normal thyroid gland is given for the size of the follicles, amount of stroma, amount of parenchyma, amount, density and vacuolization of the colloid, size of the cells, amount of mitochondria, and the amount of chromophobe and chromophil secretion antecedents in the cells.

The standards adopted are purely arbitrary, and are not mathematical in the sense that plus two means twice as much as plus one. The figures given in the tables are intended to represent the average for all sections of the specimen examined, and no account is taken of variations in different parts of the same specimen. That these variations may be extreme will be explained.

The range adopted for indicating the size of the follicles is from minus four to plus one, minus four representing the minute follicles of active fetal adenomas and plus one including all cases in which the average size of the follicles is greater than normal. The variation of the stroma is from minus one to plus three, and for the parenchyma is from minus one to plus four. In estimating the amount of parenchyma, the interstitial glandular cells, as well as the cells lining the follicles, are considered in the total. The standard used to denote the variation in the amount of the colloid is from minus four to plus one; for the density is from minus two to plus two, and for the vacuolation is from minus one to plus four. The size of the cells, the amount of the mitochondria, and the amount of the chromophobe secretion antecedent vary from minus one to plus four, and the chromophil secretion granules from minus one to plus three.

The standard adopted for the amount of each constituent in the normal thyroid gland of the adult human being is one. Consequently, the number one signifies quite large follicles well filled with colloid of moderate density, a small amount of stroma and parenchyma, and small dormant appearing cells which contain a moderate number of mitochondria for the amount of cytoplasm, occasionally a small chromophobe vacuole and, rarely, a chromophil granule. The chromophobe vacuoles in the follicles of the normal gland are few in number and small in size. The figures given in the tables are intended to represent the amount of each component as compared to the amount of the same component in the normal gland, and are each one estimated independently without regard to the other components of the specimen being

studied. The mitochondria and intracellular secretion antecedents are estimated on the basis of the average amount of each per cell without regard to the size of the cells or the cellularity of the tissue.

SIMPLE ADENOMAS

In the series, fifteen specimens were classed as simple or colloid adenomas (Fig. 13). All were definitely encapsulated tumors growing in the thyroid gland. In size, they varied from small nodules to large tumors, 10 cm. in diameter. They were often bilateral, and multiple tumors were the rule. The substance was for the most part gelatinous with small cysts and fibrosed areas scattered through the mass. In some of the older cases, calcified areas were present.

TABLE 1.—*Simple Adenomas*

Case	Age	Duration	Basal Metabolism	Size of Follicles	Amount of Stroma	Amount of Parenchyma	Amount of Colloid	Density of Colloid	Vacuoles in Colloid	Size of Cells	Mitochondria in Cells	Chromophobe Secretion in Cells	Chromophil Secretion in Cells
Normal	..	.....	....	1	1	1	1	1	1	1	1	1	1
1.....	15	3 years	— 7	—1	+1	+1	—1	1	—1	+1	+1	+1	—1
2.....	38	4 years	— 7	1	+1	1	1	1	1	—1	—1	—1	1
3.....	35	4 years	— 1	—1	+1	+1	1	+2	—1	1	—1	—1	+1
4.....	23	2 years	+ 7	+1	1	—1	+1	+1	—1	+1	+1	+1	+1
5.....	40	10 years	+11	—1	+3	+1	—1	+2	—1	1	1	—1	—1
6.....	67	10 years	+13	1	+2	+1	—1	+1	—1	1	1	1	—1
7.....	32	16 years	....	+1	+2	—1	+1	+2	—1	—1	—1	—1	1
8.....	26	3 years	....	+1	+3	—1	+1	+1	—1	1	—1	—1	—1
9.....	17	3 years	....	+1	1	1	+1	+1	+1	+1	+1	1	+2
10.....	25	3 years	....	+1	—1	—1	+1	+1	—1	+1	Degenerated, granulated and vacuolated		
11.....	24	6 years	....	+1	+3	—1	+1	+1	—1	+1	+1	1	1
12.....	31	7 years	....	1	1	1	1	+1	—1	—1	1	—1	1
13.....	40	6 years	....	+1	+3	—1	+1	+2	—1	—1	—1	—1	—1
14.....	56	5 years	+22	—2	+1	+2	—2	1	+1	+2	+2	+1	+2
15.....	45	7 years	+29	—2	+2	+2	—1	+2	1	+1	+2	+1	1
16.....	45	7 months	....	—1	+1	+1	—1	1	+1	1	1	+2	1

In duration, the tumors varied from 2 to 16 years, the average being 6½ years. In age, the patients varied from 15 to 67 years, the average being 32 years. It is unfortunate that basal metabolism determinations were made in only eight cases. However, in none of the cases in which it was omitted were any toxic symptoms noted in the clinical history or physical examination. The two definitely toxic cases with known elevation in the metabolic rate are placed at the bottom of the table (Table 1), and are treated separately in the text.

Histologically, the simple nontoxic adenomas, as a group, resemble the normal thyroid very closely, as is indicated in Table 1. The chief difference between them and the normal gland is in the size of the follicles. In the normal gland, the follicles are fairly uniform in size, while in the simple adenomas they are very irregular, the tumors as a

rule being made up of small follicles mingled with very large, dilated ones. The average size may be greater or less than normal or about normal, depending on the predominant type. But, in all cases, there is extreme variation in the individual follicles, though in some specimens localized areas are found where practically all the follicles are considerably larger than normal, while in other sections from the same adenoma the small follicles predominate. The large follicles are usually irregular in shape from mutual pressure and the encroachment of small follicles developing between them.

The stroma in one third of the cases was about normal in amount, and in the other cases it was increased to a variable extent. The increase is largely in the nature of localized areas of fibrosis and thickening of the stroma around the larger blood vessels, and is quite different from the diffuse fibrosis of exophthalmic goiter. In the fibrosed areas, large blood vessels with greatly thickened walls and lumens narrowed by endarteritic changes are often found. The fibrosed areas tend to undergo hyaline degeneration. As a rule, I attempted to avoid the obviously degenerated areas in taking tissue for examination, and so will not attempt to describe the various types of change in detail. Suffice it to say that cysts or calcification are the ultimate result in many instances. Some sections consisted of small atrophic follicles sparsely scattered through broad bands of hyaline degeneration and fibrous tissue. Hemorrhages are occasionally seen, but are much less common than in the fetal type of adenoma. Lymphoid infiltration was noted in only a few cases, and the nodules were smaller and less numerous than in the cases of exophthalmic goiter.

As the amount of parenchyma depends to a large extent on the size of the follicles, it does not vary markedly from that of the normal gland. In specimens in which the large follicles predominate, the parenchyma is slightly less than normal in amount, and in those in which the small follicles predominate it is increased. This is true even though the small follicles are filled with dense colloid. The regenerating areas (Fig. 13) in the walls of the large follicles, if unusually abundant, also may cause a definite increase in the parenchyma. These are in all respects similar to those described above in the normal gland. That is, they are papilla-like elevations of the follicle wall which project into the lumen, and are covered by cells which are higher than those lining the rest of the follicle. The cells are in a single layer and rest on the stroma, which forms the core of the papillae. In sections, there often appear to be several layers of cells covering the papillae. This appearance is largely due to the increased height of the cells, and the obliquity of the section to their long axis. However, there is a marked tendency on the part of the surface cells to wander back into the stroma and form new follicles in the base of the projection. This may result in

true reduplication of the surface layer, and all stages between surface cells and true interstitial cells can be found. Such areas were present in variable numbers in all simple adenomas studied. However, in no case were they sufficiently numerous to cause a definite increase in the amount of parenchyma. In those cases, in Table 1, in which the parenchyma is judged to be more than normal in amount, the increase is almost entirely due to the large number of small follicles present.

The colloid fills and distends the follicles as it does in the normal gland. Its amount is therefore dependent on the size and number of the follicles, and does not vary greatly from that of the normal gland. As a rule, it is more dense than normal, even in the small follicles, and in no case was it decreased in density. The vacuoles in the colloid, which are believed to indicate the presence of the chromophobe secretion, are usually smaller and less numerous than in the normal gland. The cells lining the follicles differ practically not at all from those of the normal gland. In the smaller follicles they are cuboidal, and in the large follicles they are flattened, with the exception of the low columnar cells of the areas of regeneration. Consequently, in specimens containing large numbers of small follicles, the cells average slightly larger than in the normal gland. Their mitochondrial content is about the same as that of similar cells in the normal gland, and the same is true of the chromophobe and chromophil secretion antecedents. It is to be noted, however, that occasionally one finds a rather large follicle lined by low columnar cells, practically all of which contain a number of chromophil granules, while the cells of the neighboring follicles are entirely devoid of them. The colloid cells do not vary markedly in number or appearance from those of the normal thyroid. In areas of degeneration, the cells degenerate by vacuolization and autolysis without forming colloid cells.

The interstitial cells are similar to those of the normal gland, and average about the same in number. In areas in which the large follicles predominate, they are decreased, and in areas of small follicles they are usually increased in number. They are also increased in the areas of regeneration, as was noted above.

The foregoing description is applicable to the nontoxic simple adenomas studied. Cases 14 and 15 were definitely toxic clinically, and showed moderate increase in the basal metabolic rate. These two cases will be considered separately. Cases 14 and 15 are what is usually described as regenerating adenomas. They both contain some dilated follicles with some areas of regeneration in their walls, but the predominating feature is the great number of small follicles present. These also are filled with dense colloid, and the chromophobe vacuoles are not markedly increased. The interstitial cells are increased and are apparently engaged in forming new follicles. Largely because of the

great number of small follicles, the parenchyma is definitely increased in amount and the colloid diminished in about the same proportion. The cells vary from normal to moderately tall, columnar cells, and average a little above the normal in size. The mitochondria are definitely increased and the chromophobe secretion is slightly increased in both cases. In one case, the chromophil secretion granules are increased, and in the other they are normal in number.

Case 16 was a diffuse enlargement of the thyroid of seven months' duration. It is classed as an early colloid goiter. There were no toxic symptoms noted preoperatively, but following a partial thyroidectomy there was a definite postoperative reaction of moderate severity. Histologically, the sections are fairly uniform throughout. There are a considerable number of dilated follicles filled with dense colloid, but the outstanding feature is the great increase in the number of small follicles. These also are filled with colloid of moderate density. The projections from the walls of the larger follicles, comparable to the regenerating areas of the normal gland and adenomas, are covered by cuboidal epithelium similar to that lining the rest of the follicle. No columnar cells are seen. The amount of parenchyma is greater than normal on account of the many small follicles present. The interstitial cells are slightly increased. The cells differ from those of the normal gland only in the presence of a moderate excess of the chromophobe secretion vacuoles. These are present even in the extremely flattened cells lining some of the larger follicles.

FETAL ADENOMAS

Twelve cases are classed as fetal adenomas (Fig. 12). Like the simple adenomas, they were encapsulated thyroid tumors, variable in size and often multiple. They differ from the simple adenomas in the greater frequency of interstitial hemorrhage and cystic degeneration. Calcification and extensive fibrosis, such as are common in old simple adenomas, were not seen.

In duration, the tumors varied from 6 months to 26 years, the average being 8½ years. The age of the patients varied from 16 to 55 years, the average being 37 years. Basal metabolism determinations were made in only four cases; two of these were toxic and two were not toxic. In two other cases (Cases 3 and 4), the clinical diagnosis of mildly toxic adenoma was made. Eight cases (Cases 5 to 12) were clinically nontoxic adenomas.

It has been noted by Marine and Lenhart [31] that the fetal adenomas have a period of active growth, which is followed by a resting or colloid state. In this series, the four clinically toxic adenomas consisted largely of highly cellular, actively growing tissue with minute follicles

31. Marine and Lenhart (Footnote 2, seventh reference).

containing very little thin colloid (Fig. 12). The nontoxic tumors contained more colloid and less parenchyma, and were often cystic with only a small amount of living tissue lining the wall of the cyst.

Table 2 gives the details of these tumors. The follicles average much smaller than those of the normal gland. In the actively growing tumors, the tissue consists of a mass of densely packed, minute follicles, usually circular in outline, but occasionally flattened or even long and tubular. In the less active tumors, the follicles are more or less dilated and filled with colloid. They average much smaller than those of the normal gland, though occasional widely dilated follicles are seen. In most of the inactive tumors there is wide variation in the size of the follicles in the same tumor. In some cases, however, the follicles are quite

TABLE 2.—*Fetal Adenomas*

Case	Age	Duration	Basal Metabolism	Size of Follicles	Amount of Stroma	Amount of Parenchyma	Amount of Colloid	Density of Colloid	Vacuoles in Colloid	Size of Cells	Mitochondria in Cells	Chromophobe Secretion in Cells	Chromophil Secretion in Cells
Normal	..	.....	....	1	1	1	1	1	1	1	1	1	1
1.....	33	2 years	+19	−4	+2	+4	−4	−2	+2	+2	+3	+2	+2
2.....	29	4 years	+34	−3	+1	+3	−3	−2	+3	+2	+2	+4	+2
3.....	45	1 year	....	−3	+1	+3	−3	1	+1	+2	+2	+2	+2
4.....	48	15 years	....	−4	+2	+3	−4	−1	+1	1	+1	+2	−1
5.....	22	4 years	− 4	−4	+3	−1	−3	−1	+1	−1	1	+1	1
6.....	16	6 months	+ 5	−3	+3	−1	−3	−2	+1	+1	+2	+2	1
7.....	39	5 years	....	−3	+2	+1	−3	−1	+2	+1	+2	+2	−1
8.....	50	4 years	....	−3	+4	−1	−3	−1	+1	+1	+1	+2	+1
9.....	50	22 years	....	−3	+4	−1	−3	1	+1	1	1	+1	−1
10.....	55	26 years	....	−3	+4	−1	−3	+1	−1	−1	−1	+1	+1
11.....	23	10 years	....	−3	+2	+2	−3	−1	−1	+2	+3	+2	+1
12.....	35	6 years	....	−2	+2	+1	−2	−1	+1	+1	+1	+1	−1
13.....	49	4 years	....	−1	+1	+1	−1	+1	1	+2	+3	+2	+1

small and fairly uniform but much less numerous than in the toxic cases, and one often finds areas of minute follicles sparsely scattered through a myxomatous or hyaline matrix.

The stroma is more abundant than in the normal gland and different in character. The increase in the stroma is least in the highly cellular active areas, and most in the areas of widely separated minute follicles. All transitions may be present in the same tumor. The connective tissue is delicate in structure, and, when increased, tends to be myxomatous or to become hyaline-like. The dense fibrous bands so common in simple adenomas are not seen in the fetal type. The delicate, fetal-like connective tissue surrounds the follicles and separates them more or less widely, varying with the cellularity of the tissue.

The blood vessels of the active stage are much more abundant and larger than in the normal gland. In the resting or inactive areas, they are less abundant, but are often widely dilated. In both types, the

vessels have much thinner walls than vessels of equal size in the normal gland. The thin walled vascular spaces lying in the delicate myxomatous stroma offer an explanation for the frequency of hemorrhages in these tumors.

The amount of parenchyma varies greatly in different tumors depending on the size and abundance of the follicles and the size of the cells. In the very active areas composed of minute follicles closely packed together and lined by fairly large cells, the tissue is almost completely parenchymatous. In the less active areas, the parenchyma is reduced by the accumulation of colloid in the follicles, which causes them to increase in size and the cells to become flattened, and by the increase in the stroma, which separates the follicles more and more widely until the proportion of glandular tissue may be considerably less than normal. Usually, these changes go on simultaneously, and the typical picture is that of small follicles filled with colloid and lined by flattened cells. These follicles are fairly widely separated by bands of myxomatous tissue. Or the follicles may remain minute and be sparsely scattered through the myxomatous matrix. In other cases there is little increase in the stroma, but the follicles continue to dilate until they resemble those of the normal thyroid. All types may be present in the same tumor.

The colloid is always considerably less in amount than that present in the normal gland. In the very active areas, almost no colloid is present, and in the inactive areas, although the follicles may be filled with colloid, their small size and the excess of the stroma keep it well below the average for the normal gland. In density, it varies from very thin in the active areas to moderately dense colloid in the inactive tumors. The chromophobe vacuoles in the colloid are nearly always larger and more abundant than normal, even in the thin layer of follicles lining the cysts.

The cells vary in size with the activity of the tissue. In the active tumors, they are definitely larger than those of the normal gland and contain a large vesicular nucleus (Figs. 2-6). Those lining the small circular follicles are pyramidal in shape, while those lining the tubular follicles are cuboidal or even quite high columnar, and resemble the cells of an exophthalmic goiter. In the inactive tumors, the cells may be flattened and average definitely below the normal in size, but they usually are equal to, or slightly larger than, those of the normal gland. In some of the cystic tumors, they are quite large and resemble those of toxic glands.

The mitochondria are, as a rule, more abundant than in the cells of the normal gland. In the active tumors, they are markedly increased and equal to those in many cases of exophthalmic goiter. The short rods and granules are somewhat thicker than those of the normal gland,

and often fill the entire protoplasm with a dense mass of granules (Fig. 4). In the taller columnar cells, the long threadlike mitochondria are seen (Fig. 5). The number varies directly with the size of the cells, but the mitochondria also are more concentrated in the protoplasm of the larger, more active cells. Even in the walls of the cysts or other inactive tumors with cells of normal size, the mitochondria are numerous. They are scattered irregularly through the cytoplasm, but exhibit a slight tendency to be concentrated in the basal zone of the cell.

The chromophobe secretion antecedent, as evidenced by the small clear vacuoles in the cells, is increased in all the cases studied. In the active tumors, the increase is marked, and the vacuoles exhibit a tendency to be localized in the apical zone of the cell (Fig. 5). In the flattened or cuboidal cells of the less active areas, the vacuoles may be found in any portion of the cytoplasm, just as they are in the normal gland. It is to be noted, however, that, regardless of the type of cell, they are increased above the number usually found in the normal gland cells.

The chromophil secretion granules are usually definitely increased, and, in three of the active tumors, the increase is marked. In these tumors, the granules are very minute and are collected in the apical zone of the pyramidal cells near the lumen of the minute follicles (Fig. 6). In the inactive tumors with larger follicles filled with colloid and lined by cuboidal cells, the secretion granules are larger and are apt to be found in any portion of the cell protoplasm. In very inactive areas, as evidenced by small colloid filled follicles widely separated by an abundant stroma, colloid droplets are occasionally found in a large percentage of the cells. They are irregularly ovoid in shape and stain as do the chromophil secretion granules, but are much larger. In most of the adenomas examined, no intracellular colloid was noted.

The interstitial cells resemble those of the normal gland. In the cellular areas, they are markedly increased, are actively forming new follicles, and all stages from isolated cells through two or more cells around a minute droplet of colloid up to the typical follicles can often be seen in the same field. In the inactive areas, the interstitial cells are about normal or decreased in number. In areas of small, dilated follicles lined by dormant looking, flattened cells, the interstitial cells may be almost completely absent.

Colloid cells are rarely seen in fetal adenomas. The cells tend to degenerate by vacuolization of the cytoplasm and by autolysis. This type of degeneration affects areas of tissue rather than single cells in the walls of healthy follicles. The degeneration vacuoles are easily distinguished from the chromophobe secretion vacuoles since they occur throughout the cytoplasm, and are accompanied by other changes in the cell: the nuclei are pyknotic; the mitochondria are fragmented, vesi-

cular or absent, and the cytoplasm is fuchsinophilic. A narrow zone of such cells is usually found around the edge of the section. It is caused by the trauma of cutting the fresh tissue.

CASES OF EXOPHTHALMIC GOITER

In the series of sixty-five cases, there are thirty-three that are classified as exophthalmic goiter. They all exhibit diffuse hypertrophy and hyperplasia in varying degrees. One or more basal metabolism determinations were made previous to operation in all cases. In Table 3, only the last determination before operation is given. The rate was

TABLE 3.—*Exophthalmic Goiter*

Case	Age	Duration	Basal Metabolism	Size of Follicles	Amount of Stroma	Amount of Parenchyma	Amount of Colloid	Density of Colloid	Vacuoles in Colloid	Size of Cells	Mitochondria in Cells	Chromophobe Secretion in Cells	Chromophil Secretion in Cells
Normal	..	.....	....	1	1	1	1	1	1	1	1	1	1
1.....	45	6 years	+17	−3	+1	+3	−3	−2	+2	+3	+4	+3	+1
2.....	30	4 years	+20	−2	+1	+3	−2	−1	+3	+3	+3	+3	1
3.....	23	8 years	+27	1	1	+1	−1	−1	+1	+2	+2	+2	1
4.....	38	10 years	+27	−3	+3	+3	−2	1	+2	+3	+3	+3	+1
5.....	41	5 years	+31	1	+2	+2	−1	+1	+2	+2	+2	+2	+2
6.....	31	14 years	+32	−2	+1	+3	−3	1	+3	+3	+4	+4	+1
7.....	41	4 years	+32	−1	+1	+2	−1	−2	+2	+2	+2	+3	+2
8.....	26	2½ years	+34	−3	+3	+3	−4	1	+3	+3	+4	+3	+1
9.....	39	10 years	+34	−3	+3	+3	−3	−2	+2	+2	+2	+3	+3
10.....	41	1 year	+35	−3	+2	+3	−3	+1	+2	+2	+3	+2	+1
11.....	29	4 years	+35	−4	+2	+4	−4	−1	+2	+3	+3	+2	+2
12.....	51	8 months	+37	1	+1	+2	−3	−1	+4	+3	+4	+3	1
13.....	23	6 months	+39	−3	+1	+4	−3	−2	+2	+4	+4	+2	1
14.....	35	5 years	+39	1	1	+1	−1	−2	+1	+1	+2	+3	+2
15.....	29	1 year	+41	−3	+1	+3	−4	−1	+2	+4	+4	+3	+1
16.....	48	4 years	+41	−2	+1	+3	−3	−1	+3	+3	+3	+3	1
17.....	44	8 years	+42	−2	+1	+3	−2	−1	+3	+2	+3	+3	+3
18.....	48	4 years	+44	−3	+2	+4	−4	−2	+2	+4	+3	+2	−1
19.....	49	1½ years	+45	−2	+1	+3	−3	−2	+3	+4	+4	+4	+1
20.....	46	10 years	+46	−3	+3	+3	−2	1	+1	+2	+3	+3	+3
21.....	34	2 years	+49	+1	1	+3	−3	−2	+4	+4	+4	+4	−1
22.....	50	1½ years	+51	+1	1	+1	−3	−2	+4	+1	+3	+4	1
23.....	43	4 years	+52	−2	+1	+3	−3	−1	+2	+3	+4	+3	+1
24.....	33	2 years	+58	−2	+1	+3	−3	−1	+3	+3	+4	+4	−1
25.....	34	8 years	+56	−2	+1	+3	−3	−1	+2	+4	+4	+3	+3
26.....	43	4 months	+57	−2	+1	+2	−2	−1	+2	+3	+2	+4	−1
27.....	38	10 years	+65	−2	+2	+3	−3	−1	+3	+4	+4	+3	−1
28.....	43	2 years	+65	−1	+1	+3	−3	−2	+3	+3	+4	+3	−1
29.....	38	6 months	+68	−3	+2	+4	−3	−2	+2	+4	+4	+3	1
30.....	46	13 months	+70	−2	+1	+2	−2	−2	+1	+3	+4	+4	1
31.....	46	9 months	+78	−3	+1	+3	−3	−2	+2	+3	+4	+4	+1
32.....	35	7 years	+86	1	+2	+3	−4	−2	+4	+4	+4	+4	1
33.....	35	3 years	+88	−3	+1	+4	−4	−1	+2	+2	+2	+4	+2

increased in all cases and varied from 17 to 88 per cent. above the normal, the average being 48 per cent. In age, the patients varied from 23 to 59 years, the average being 41 years. It is difficult to ascertain the duration in many cases; however, as accurately as it could be determined, it varied from 6 months to 14 years, the average being 4 4 years.

On the whole, the clinical picture agreed very well with the metabolic findings. That is to say, the patients with the more pronounced

toxic symptoms usually were found to have a marked elevation in the basal metabolism. The pathologic picture, however, did not present any definite characteristics by which the degree of toxicity could be accurately judged. A study of Table 3, in which the cases are arranged in an ascending order on the basis of the basal metabolism, disclosed the general trend of the mitochondria and chromophobe secretion to be greater in the more toxic cases, but many exceptional cases present themselves which do not follow any rule. The same is true in regard to the relation of the pathologic findings to the duration of the disease. As a rule, the early cases were extremely cellular, but many old cases were quite cellular also. On pathologic findings, it has not been possible to classify them definitely. Consequently, the group will be described as a whole, and the details of the individual cases are given in Table 3.

The follicles vary greatly in size in different glands (Figs. 14 and 15), and in different portions of the same gland. In cellular areas, they are markedly below the normal in size. This reduction is accomplished by extreme overgrowth of parenchyma which tends to obliterate the lumens of the follicles, and by the presence of great numbers of small follicles, which in some cases simulate those of active fetal adenomas (Fig. 15). In other glands, the follicles are widely dilated and average definitely above the normal size. A feature which many of these glands have in common with the simple adenomas is the presence of the widely dilated follicles in glands in which the average size is below the normal on account of the presence of large numbers of small follicles. The average size of the follicles for the series is well below normal.

The larger follicles are often exceedingly irregular in outline on account of the numerous outgrowths from the wall which project into the lumen. These papillae often have numerous secondary or tertiary papillae projecting from them, and result in follicles of most bizarre shapes (Fig. 16). In other very active areas, the follicles are quite regular in outline and fairly uniform in size. The follicles whose lumina are nearly obliterated by the overgrowth of parenchyma are often long and tortuous.

The stroma is practically always increased in amount and more fibrous than that of the normal gland. Its arrangement is similar to that of the normal gland, but broad fibrous bands traverse the gland in all directions and give it a distinctly lobulated appearance. The increase is in the nature of a diffuse fibrosis, and, in this respect, is quite different from the irregular fibrosed areas of simple adenomas which appear to be the result of localized degeneration. The stroma is, as a rule, fibrous and quite different from the delicate myxomatous-like stroma of the fetal adenomas, though one case (Case 33) contained many very cellular

areas in which the stroma resembled that of an active fetal adenoma. In glands that have been subjected to operative procedure (ligations) or to numerous roentgen-ray treatments sometime previous to examination, broad irregular localized areas of fibrosis may be found which resemble those of the simple adenomas. The fibrous stroma is present in the early cases as well as in the old ones, and there is little tendency to a progressive fibrosis of the gland; that is, the amount of stroma in many of the old cases is not in excess of that present in other fairly early cases.

In the stroma are the blood and lymphatic vessels which are markedly increased in size and number in all cases studied. The stroma extends throughout the large papillae present in many cases, and carries capillaries and lymphatics to the zone directly beneath the layer of epithelial cells covering the projections. In many cases, these minute vessels are seen to be distended by clear vacuole-like areas which strongly suggest the chromophobe vacuoles in the colloid of the follicles. In no case was it possible definitely to identify colloid in the vessels.

Lymphoid infiltration of the stroma is often present to a marked degree, though no relation between the amount of lymphoid tissue and the activity of the gland, as indicated by the basal metabolic rate, could be detected. The lymphoid infiltration may be present in early cases, but is usually more marked in the old cases, and is most marked in glands which have been injured surgically or by roentgen-ray treatments. Definite lymph follicles may be formed and so infiltrate the glands as to isolate completely small follicles or areas of parenchyma. The cells of these isolated areas are smaller and less active in appearance than the average for the gland in question. In many cases, no lymphoid infiltration was noted.

There are usually a few fat cells scattered here and there in the stroma. The interstitial cells will be mentioned below.

The amount of parenchymatous tissue present is increased in all cases though the degree to which it is increased bears no relation to the activity of the gland. As a rule, the early cases show the most marked increase in parenchyma but highly cellular areas are often found in cases of several years' duration. Also, early cases, such as Case 12 of only 8 months' duration, may consist of widely dilated follicles and, consequently, only a moderate increase in parenchyma.

The increase in the parenchyma is due to four factors: (1) increase in the size of the cells; (2) increase in the number of the follicular cells; (3) increase in the number of interstitial cells, and (4) the presence of great numbers of small follicles. The increase in the size of the cells is present in all cases. The increase in the number of cells lining the follicles causes the obliteration of the lumen or the irregular dilated follicles with numerous papillae. Increase in the interstitial

cells may be very marked and cause the collapse of many follicles. In other cases, interstitial cells may be almost completely absent and the tissue composed of closely packed follicles of various sizes. The small follicles may dominate the picture.

Any of the foregoing changes may dominate the picture, or all may be present in varying degrees in the same gland. It is not possible to associate any type with marked or slight toxic symptoms. The early cases, as a rule, show marked hypertrophy of all glandular cells with increase in the number of follicles and interstitial cells, resulting in a highly cellular tissue. In Case 29 of six months' duration, the interstitial cells are enormously increased. The older cases usually show well formed follicles with small numbers of interstitial cells, but may contain highly cellular areas, similar to those in the early cases.

The colloid is decreased in amount in all cases, and is nearly always decreased in density. The vacuoles in the colloid representing the amount of chromophobe secretion in the follicles are increased in all cases, and may almost entirely replace the colloid. The decrease in the amount of the colloid is due either to the increase in size and number of the chromophobe vacuoles or to the increase in the parenchyma. The increase in the amount of parenchyma may result in many small follicles, or may cause more or less obliteration of the follicular lumen from collapse of the empty follicles, or the encroachment of numerous papillae. Many of the very active glands consist largely of widely dilated follicles which appear empty, with the exception of a small irregularily stellate islet of thin colloid in the center from which thin strands of colloid radiate toward the follicle walls. Other equally active glands consist to a great extent of quite large follicles filled with very thin colloid and containing only a slight excess of chromophobe vacuoles. In the old cases, follicles filled with quite dense colloid are often seen.

The glandular cells are increased in size and number in all cases, but no constant relation between the degree of hypertrophy or hyperplasia and the degree of toxicity could be made out. As a rule, the increase in size is most marked in the early cases, in which tall, columnar cells are the dominant type. In the more advanced cases, the follicles are larger and the cells usually low columnar or cuboidal in form. However, many very large dilated follicles are seen which are lined by columnar cells 25 microns or more in height, and this type may dominate the picture, as in Case 32 (Fig. 16). The smaller follicles are usually lined by flattened cells of about the normal size, and these may dominate the picture, as in Case 22, which clinically was a very toxic gland (also Case 14, Fig. 14). These flattened cells may present evidences of extreme activity, as will be explained. The nuclei are more vesicular and larger than those of the normal gland, but in the majority

of cases the increase in the size of the nucleus is proportionately less than the increase in the amount of cytoplasm. Mitotic figures are occasionally seen in the highly cellular areas.

In spite of the evident hyperplasia present in most cases, the cells lining the follicles always tend to remain in a single layer, and to remain with their bases resting on the delicate stroma which follows all the irregularities in the follicular walls. The tall columnar cells often have their nuclei at different levels, and thus give an erroneous impression of stratification of cells just as do areas cut obliquely to the long axis of the cells. In this series, there were no glands such as those described by Kocher [32] in which the follicles were lined by three or four layers of cells. The mosaic of intercellular cement substance or colloid is especially well seen in areas of tall columnar cells cut transverse to the long axis and near the apex of the cell.

The mitochondria are definitely increased in all cases. Not only is there an absolute increase due to the greater size of the cells, but there is also a relative increase due to their greater concentration in the cytoplasm. As a rule, they are slightly larger than those in the normal gland cells and in the tall columnar cells may be long and tortuous, single filaments often extending from the basal to the apical zone. In some very active glands in which the cells contain large numbers of chromophobe vacuoles, the mitochondria are very minute rods and granules irregularly scattered between the vacuoles (Fig. 11). In these cells, also, the mitochondria are more tortuous, and branch in an irregular manner. In other instances, they so crowd the cytoplasm that it is almost impossible to differentiate the individual granules and filaments. Apparently, they are not concentrated in any special zone of the cell, but are found throughout the cytoplasm wherever space is available. In most of the tall columnar cells, the nucleus lies in the basal half of the cell; consequently, here the mitochondria are more numerous in the apical region. In others in which the cells are crowded together, many of the nuclei are in the apical zone and the mitochondria are concentrated in the basal zone. Also, in cells in which the apex is filled with secretion vacuoles, the mitochondria are relatively few in number in the apical zone. There is no constant relation between the amount of the mitochondria and the toxicity of the gland. They are increased in all cases, but the increase may be very marked in relatively mild cases, such as Case 1, and only moderate in very active cases, such as Case 33 (Figs. 7, 9 and 11).

The chromophobe vacuoles in the cells are markedly increased in all cases, and may be so numerous in certain cells that the mitochondria are of necessity decreased in amount on account of lack of space (Fig.

32. Kocher (Footnote 2, ninth reference).

7). In the tall columnar cells, the chromophobe vacuoles frequently fill the entire apex of the cell, causing it to assume a bulbous form and project into the follicles (Fig. 18). In the cuboidal cells, the vacuoles are scattered irregularly through the cytoplasm, and may be very numerous in small flattened cells. Occasionally, high columnar cells are seen whose basal zone is filled with chromophobe vacuoles. When abundant in a cell, the vacuoles often fuse to form a few very large vacuoles. Occasional cells are seen in which the vacuoles apparently are rupturing into the follicle. The fact that the vesicles with a limiting membrane are rarely seen in the follicles suggests that the intact vacuoles are not often discharged. The chromophobe vacuoles are usually definitely more numerous in the cells of the very toxic glands than in those of the milder cases.

The chromophil secretion granules vary in number from less than the normal to marked increase above the normal (Figs. 10, 19 and 20), and the variation is totally independent of the activity of the gland or of the type of tissue present. In general, they are increased in the cases of long duration, and normal or less than normal in the early cases. They are usually fairly large granules lying in the body of the cell, between the apex and the nucleus. Very rarely, what appears to be one of these granules is seen in the lumen of a follicle.

Apparently, the mitochondria remain in the cells and the chromophobe and chomophil secretion antecedents are discharged into the follicles. The process is not a rhythmic one, but apparently proceeds independently in each cell, as cells in all stages, varying from those containing no secretion antecedents to those containing a very large amount, may be present in the wall of the same follicle.

The canalicular apparatus does not differ in form or location from that of the cells of the normal gland. It is, however, slightly larger and more easily demonstrated on account of the increase in the size of the cells. It is usually found between the nucleus and the apex of the cell, but occasionally is found lateral to the nucleus or even in the basal zone. In the interstitial cells, it is simply near the nucleus, there being no apical or basal zone.

There is a phenomenon of fairly common occurrence in some very active glands by which some mitochondria are discharged into the follicles. This is the shedding of the entire apexes of the columnar cells into the follicles (Figs. 8 and 21). The process is apparently accomplished by an annular constriction of the cytoplasm in the zone between the apex and the nucleus which proceeds until the distal portion is completely separated and shed into the follicle. The process is unusually general for the cells of the follicle in which it occurs, and all stages can be seen in the cells lining a single large follicle. The cast-off apexes

assume a spherical form, and are seen in the thin colloid as basophilic spherules containing chromophobe vacuoles and fuchsinophilic granules. They are easily distinguished from the degenerating desquamated follicular cells or blood cells so often found in the follicles.

The interestitial cells (Fig. 9) resemble the follicular cells of the gland containing them in the abundance of their secretion antecedents and mitochondria. As stated, they may be greatly increased or almost entirely absent. In cellular areas in which they are numerous, they seem to be largely follicular cells that wander back into the stroma, as cells in all stages of the process can often be seen in a single field. The appearance can, of course, be interpreted as interstitial cells migrating into the follicular wall, but, as it only occurs in regions of marked hyperplasia of the follicular cells, the former view seems to be the more reasonable one. When numerous, the interstitial cells are actively engaged in the formation of new follicles, and all stages of the process may be present in a single field. Occasionally, greatly hypertrophied interstitial cells are seen. They resemble the other cells of the gland except that they are from four to six times as large as the average, and their single nuclei are from three to four times the average size. Rarely, such cells are present in the walls of the follicles.

Fuchsinophilic cells that resemble the average cells of the gland in size and form occur quite commonly in many of the glands, and in others are entirely absent. They are more common in the cases of long duration, and may be either interstitial or follicular in location. They occur singly or in groups, varying from two to three cells to large islets 1 cm. or more in diameter, in which practically all the cells are of this type (Fig. 22). All transitions between them and the typical cells of the gland can be traced. Their cytoplasm is densely packed with small fuchsinophilic granules which do not blacken with osmic acid and are apparently mitochondria. Secretion vacuoles and granules are rarely present in these cells. Their nuclei are not pyknotic, but are less vesicular than those of the average cells of the gland.

Colloid cells, both homogeneous and granular types, are very common in most cases. They are most abundant in very cellular areas and seem to be degenerating cells whose death has been caused by the pressure of neighboring cells. They occur singly and in small groups.

MALIGNANT TUMORS

Two cases of malignant tumor occurred in the series. One was a small round cell sarcoma which had so infiltrated the thyroid that the gland structure was almost obliterated. The thyroid tissue was limited to scattered follicles lined by inactive or degenerating cells. The tumor cells resembled lymphoid cells, but were slightly larger and contained

larger and more numerous mitochondria than normal lymphocytes. Mitotic figures were numerous. The other tumor was an adenocarcinoma of the thyroid. Histologically, it was highly cellular and composed of small follicles, many of which were long and tortuous. The majority of the follicles were empty. Some were filled with dense colloid. The scanty stroma was myxomatous in character. The cells were about twice the normal size with large vesicular nuclei and abundant mitochondria. The chromophobe secretion was less than normal in amount, and no chromophil granules were seen. Mitotic figures were present but not numerous.

COMMENT ON SECRETORY PHENOMENA

I agree with Bensley [8] that the secretory granules described in the thyroid cells by all investigators previous to 1914 were, in part at least, poorly fixed and stained mitochondria. Furthermore, in no case was any attempt made to differentiate these so-called secretion granules from the mitochondria in the cells. With the demonstration of mitochondria in the thyroid cells, it is not possible to accept any of the old observations on secretory granules in these cells. This narrows the field of discussion down to those intracellular secretory antecedents which have been differentiated from mitochondria. These are the colloid droplets of Biondi,[9] the chromophobe secretion of Andersson,[12] the granules noted in the hyperplastic glands of the opossum by Bensley [21] in 1914, the secretory antecedent of Bensley [8] (1916), and the chromophobe vacuoles and chromophil granules reported by Key [33] in 1921 and studied in more detail in this paper.

The so-called colloid cells of Langendorff [10] are obviously senile cells, and are not to be considered as having any physiologic activity, though it is probable that the degenerating cell bodies are shed into the follicles and add to the bulk of the colloid.

The intracellular colloid droplets, first demonstrated by Biondi,[9] have been noted by many subsequent investigators. Because of their rarity in normal and hyperactive glands, it has long been suspected that these droplets were not the normal secretory products of the cells. In 1914, Bensley [21] clearly demonstrated that the intracellular colloid is not a normal secretory antecedent, but is a storage product and evidence of hypo-activity on the part of the cell containing it.

The minute granules described in hyperactive thyroids of the opossum by Bensley differ from the chromophil granules to be mentioned below, in that they were not darkened by osmic acid. Dr. Bensley [34] now doubts

33. Key, J. A.: Secretory Phenomena in Pathological Human Thyroids, Anat. Record **23**:23, 1922.

34. Bensley, R. R.: Personal communication to the author.

that they are secretory antecedents. I have not identified them in any of the glands studied.

The secretion antecedent of Bensley,[8] demonstrated in formaldehyd Zenker material as vacuoles in the basal zone of the cells, whose contents are stained faintly by Wasserblau, have not been seen by any other investigator. I have repeated Bensley's technic on a number of hyperactive human thyroid glands, and have obtained pictures similar to those described by him. However, in the light of the foregoing observations, I interpret them differently. In my experience, in formaldehyd Zenker material, the chromophobe vacuoles and the mitochondria are not well preserved. The secretion antecedent of Bensley is, I believe, the basophilic cytoplasm of the basal zone of the cell which, owing to the action of the fixing fluid, appears to be segregated into vacuoles.

The chromompil granules described above are probably lipins on a protein base (liposomes). They give reactions for fat and for protein, and when chromated stain with many stains. If insufficiently chromated, they may appear as rings or crescents. Their location in the apical zones of the cells, their similarity to the colloid in staining reactions, and the fact that similar granules are occasionally seen in the follicles, lead me to believe that these chromophil granules are discharged into the follicles. In this sense, they are a secretion antecedent. However, the number of these granules present in the cells bears no relation to the activity of the gland as indicated by the basal metabolism and clinical picture. Consequently, I do not believe that they contain the active constituent of the thyroid secretion.

The water-like secretion antecedent described above is, I believe, identical with that described by Andersson,[12] though his data are insufficient to make the identification positive, and differ from my observations in certain details. I have called it chromophobe secretion after Andersson. Dr. Bensley [34] does not believe that these vascuoles are a part of the mechanism of secretion. He regards them as water discharged by the hydrophilic colloids of the cell, which are in a critical state and may be made to discharge or absorb water by slight changes in the salt content of the surrounding fluid. The same is true, in his opinion, of the vacuoles in the follicles.

I have identified these chromophobe vacuoles in the cells and in the follicles of every thyroid gland studied, and have found that in size and number they vary directly with the activity of the gland, as indicated by the clinical picture and the basal metabolism. For this reason, I believe that they indicate the presence of a thin watery fluid which contains the active constituent of the thyroid secretion. As stated above, it is possible in the case of the intracellular vacuoles and very probable in the case of the large intrafollicular vacuoles, that the pictures seen in the

sections are not identical with the condition present in the living gland. In the living gland, it is probable that the vacuoles in the colloid are present as areas of increased fluidity rather than as clear-cut vacuoles with sharply defined margins. This condition, however, does not alter their importance in the least. The crucial point is that in every hyperactive thyroid studied the intracellular chromophobe vacuoles were increased and either the intrafollicular vacuoles were increased or the colloid was homogeneous and much less dense than in the normal gland.

I do not believe that either the chromophobe vacuoles or the chromophil granules arise directly from the mitochondria. All three are independent cytoplasmic constituents, and do not arise from one another or from the nucleus. The mitochondria are increased in the cells of hyperactive glands because these cells are larger, better nourished and probably are consuming more material than the cells of the normal gland. The mitochondria are not secretion antecedents, and do not pass into the follicles except in the instances noted in which the intact apexes of the cells are cast off. They are present in practically every living cell, plant and animal, and probably have some function in connection with the general metabolism of protoplasm. What that function is, is not known, and the present investigation throws no light on it. From the results of a series of starvation and feeding experiments (unpublished), I am inclined to believe that the mitochondria are food substances in the cell.

The observations of Cowdry [23] in regard to the occasional presence of the Golgi net in the basal zone of thyroid cells is confirmed for human material, but it is not felt that our present knowledge of this structure is sufficient to warrant the conclusion that its location is an indication of the secretory pole of the cell.

From the observations presented, it is believed that the normal mechanism of secretion in the thyroid gland is as follows: Chromophobe vacuoles and chromophil granules are formed in the follicular cells and discharged into the follicles. In the follicles, the granules are dissolved in the watery-like fluid of the vacuoles, and the resulting mixture is the colloid. The secretion reaches the circulation by being forced back between the follicular cells by intrafollicular pressure, and not through permanent channels or by rupture of follicles.

The interstitial cells are active glandular cells of the same type as the follicular cells, and pour their secretion out into the surrounding stroma where it may be absorbed or form the nucleus for a new follicle. The new follicles are formed by the interstitial cells collecting around a small droplet of secretion or colloid.

In the foregoing theory, the watery chromophobe substance is believed to contain the active constituent of the gland, and the chromo-

phil substance is inactive and serves as a thickening menstruum to hold the secretion in the follicles. The density of the colloid varies directly with the amount of the chromophil secretion. It is probable that the dense colloid is not forced back between the cells, but remains in the follicles indefinitely as a storage product until it is dissolved and carried away by an excess of chromophobe secretion. In this sense, secretion of chromophobe material may proceed at the normal rate and the fluid pass back into the circulation without becoming mixed with the mass of colloid in the follicle. The paucity of the secretion antecedents in the cells of the normal thyroid suggests that the process is a very slow and continuous one.

Anatomically, the foregoing theory fits in beautifully with the clinical and pathologic findings in cases of hyperthyroidism. But, from the standpoints of the chemist and the physiologist, there are certain discrepancies which will be pointed out.

It has long been known that the thyroid contains iodin, and it has long been suspected that the active principle of the gland was an iodin containing substance. Recently, Kendall [35] has succeeded in isolating in crystalline form an iodin containing compound (thyroxin) which is believed to be the active principle of the thyroid secretion. The question of whether thyroxin is the true hormone of the gland or merely a powerful pharmacologic agent has not yet been definitely settled. For instance, Plummer [36] finds that after a single dose of thyroxin sufficient to bring the basal metabolism to normal, the physiologic status of a thyroidless individual becomes normal in from ten to twelve days, and returns to the preexisting status in from five to seven weeks. Cannon,[37] on the other hand, finds that stimulation of the thyroid by gentle massage causes a definite increase in the rate of the denervated heart. The maximum effect is developed in from thirty to sixty minutes, and then passes off slowly (one-half hour). Likewise, the toxic reactions after operations for the partial removal of exophthalmic goiter occur very soon after the operation.

It is agreed by all investigators that exophthalmic goiters contain much less (usually from 5 to 10 per cent. as much) iodin per gram

35. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodin, Which Occurs in the Thyroid, J. A. M. A. **64**:2042 (June 19) 1915; Isolation of the Iodin Compound Which Occurs in the Thyroid, J. Biol. Chem. **39**:125, 1919. Kendall, E. C., and Osterberg, A. E.: The Chemical Identification of Thyroxin, J. Biol. Chem. **40**:265, 1919.

36. Plummer, H. S.: The Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body, J. A. M. A. **77**:243 (July 23) 1921.

37. Cannon, W. B., and Smith, P. E.: Some Conditions Affecting Thyroid Activity, Endocrinology **4**:386, 1920.

weight than do normal thyroids, and it is probable, though not yet demonstrated, that the substance of the normal thyroid is more active pharmacologically than is that of hyperactive glands. This is explained by the assumption that, in the normal gland, the secretion is stored, but that, in the hyperactive gland, it is transported almost as rapidly as it is formed. However, a glance at a section from an exophthalmic goiter gland convinces one that it contains many times as much of the watery chromophobe material as does a normal thyroid.

If we accept the foregoing evidence that this chromophobe material contains the active hormone of the gland, then we are forced to believe that the normal colloid, and with it the thyroxin, is not the normal secretion, but a storage material of inspissated secretion in which the hormone is probably highly concentrated and possibly held by chemical bonds which render its action much slower and more prolonged than that of the normal secretion.

SIMPLE ADENOMAS

Simple adenomas are tumors that reproduce closely the structure of the normal gland. Their chief characteristics are the production of new follicles, and the presence of many widely dilated follicles. The cells resemble those of the normal gland. It is unfortunate that only two toxic specimens were available. These were characterized by an increase in the amount of the parenchyma without a marked change in the character of the cells. On account of the great number of small follicles present, the cells were slightly larger and contained more mitochondria than the average for the normal gland. No conclusions can be drawn from such a small number of specimens, but it is suggested that the activity in the simple adenomas is directly proportional to the amount of parenchyma present. The simple adenomas differ definitely from the fetal adenomas, and it is not believed that they arise from fetal rests. They probably begin as the small nodules of thyroid tissue first described by Hitzig,[38] and later studied by Michaud.[39]. Aschoff's school [40] believe that the adenomas take their origin from the rests of the central canals of the fetal gland.

FETAL ADENOMAS

Fetal adenomas are tumors whose parenchyma and stroma resemble those of the fetal gland, and it is possible that they arise from fetal

38. Hitzig, T.: Histologie und Histogenese der Struma, Arch. f. klin. Chir. **47**:464, 1894.

39. Michaud, L.: Die Histogenese der Struma nodosa, Virchows Arch. f. path. Anat. **186**:422, 1906.

40. Klose, H.: Die pathologischen Grundlagen der Basedow'schen Krankheit, Beitr. z. klin. Chir. **102**:1, 1916.

rests, as was believed by Wolfler. It is equally possible that the small nodules of cuboidal cells with dark nuclei described by Hitzig,[38] Michaud[39] and Klose[40] represent beginning fetal adenomas. It is to be emphasized, however, that if such is the case a metaplasia of the gland cells and of the connective tissues as well must occur, because, as has been pointed out, in the fetal type of adenoma, not only are the parenchymatous cells different from those of the normal gland but definite differences also exist in the stroma and in the blood vessels. In the actively growing stage of a fetal adenoma, the gland cells are larger than normal and contain an excess of both types of secretion and of mitochondria. It is probable that the activity of the tumor varies directly with the amount of active parenchyma present. Tumors may contain areas of very active tissue and no symptoms arise unless a considerable amount of such tissue is present. Increase in the amount of mitochondria in a cell is evidence of increased activity on the part of that cell, but it is not evidence of the toxicity of the tumor because the active area may be very small. In Case 11, Table 2, the microscopic appearance was that of a toxic adenoma, but the tumor was a small cyst, and there was only a thin layer of active tissue lining the cyst wall.

EXOPHTHALMIC GOITER

Exophthalmic goiter is characterized by a generalized hyperplasia and hypertrophy of the parenchyma and stroma. The parenchyma cells, especially in the early cases, are increased in size and the nuclei are larger and more vesicular than normal. This condition of the cells suggests that the thyroid in these cases is reacting to some continuous stimulation, and that, although its increased activity is probably the cause of most of the symptoms, the ultimate cause of the disease is the cause of the stimulation. From the material at my disposal, I have seen no evidence that, in exophthalmic goiter, the change begins locally in the rest of the central canals and then extends throughout the gland, as has been described by Klose.[40]

In my series, the glands of the earlier cases were much more uniform in structure than were those of the older cases.

In the cells, the chromophil granules may be decreased but are usually normal or slightly increased in amount. The chromophobe vacuoles are always markedly increased. The mitochondria are usually markedly increased, but their increase is not always proportional to the increase in the basal metabolism. There was no evidence of any new secretory antecedent. This leads me to agree with Holst[41] that there is no evidence that in exophthalmic goiter the thyroid elaborates a special toxin which is not present in the normal thyroid.

41. Holst, J.: Untersuchungen über die Pathogenese des Morbus Basedowii, Acta chir. Scandinav., Supplement 4, p. 1, 1923.

Holst [41] divides toxic goiters into (1) primary Basedow (exophthalmic goiter) and (2) secondary Basedow (toxic adenoma, diffuse colloid goiter, cancer of the thyroid and thyroiditis).

He apparently regards the toxic symptoms in all these conditions as being due simply to an increase in the amount of the thyroid epithelium, and takes no cognizance of any change in the character of the epithelial cells themselves. All are primary thyroses, caused by epithelial tumors of the thyroid (Sie sind alle primäre Thyreosen, verursacht durch epitheliale Geschwulste der Schilddrüse).[41] With this I do not agree, but believe that, in simple adenoma and in diffuse colloid goiter, the cells resemble those of the normal gland and toxic symptoms, if present, are due to an increase in the amount of epithelium, which is essentially normal in character. In active fetal adenoma, there is an abnormal type of cell produced which is more active than the normal cell, and a smaller amount of such tissue is necessary for the production of toxic symptoms. In both types of adenoma and in diffuse colloid goiter, the degree of toxicity is roughly proportional to the amount of active tissue present. Exophthalmic goiter, on the other hand, in the beginning is probably not so much a production of new cells as it is a speeding up of activity of the cells of the normal gland. As the colloid is absorbed and the blood supply is increased, the cells hypertrophy and multiply. By the time the patient comes to operation, one may examine a number of sections of the gland and not find a single normal thyroid cell. In exophthalmic goiter, the toxic symptoms are not proportional to the amount of tissue present as some relatively small glands are very toxic, while, in other instances, the thyroid may be markedly enlarged and yet the patient may be only moderately toxic. Just how much the constitution of the individual has to do with the severity of the clinical picture, we as yet have no means of determining, but it is undoubtedly an important factor in the disease.

It is further to be noted that while in exophthalmic goiter the pathologic picture is characteristic of the disease, it gives little evidence of the degree of activity of the gland. In general, the early cases are highly cellular, and the late cases often contain follicles filled with dense colloid. However, highly cellular areas may occur in cases of long duration; and this is what one would expect from the cyclic course of the disease.

Four of the patients, Cases 22, 27, 8 and 9 of the exophthalmic goiter group had three, seven, ten and sixteen roentgen-ray treatments, respectively, before operation. In the first case, no effect on the gland could be noted in the pathologic examination. In the other three, localized areas of fibrosis were present, which were quite different from the fibrosis of the usual exophthalmic gland. These are all cases which

failed to subside under roentgen-ray treatment, and it is not possible to draw any definite conclusions. However, the fibrotic areas accompanied by local disorganization of the tissues are strongly suggestive of old focal necroses. There is certainly no alteration in the cytology which suggests a tendency to revert to the normal type, as has been described in glands subjected to ligations.[42] It is thus probable that roentgen-ray treatment benefits many of these cases by causing focal necrosis and reducing the amount of the parenchyma rather than by altering its character.

Four patients, Cases 6, 22, 32 and 33 of the exophthalmic goiter group, died from postoperative reaction. All the glands contained a large excess of chromophobe secretion. This thin, watery substance is probably very easily forced out into the circulation by manipulation of the gland, and this is believed to be the cause of the reaction.

In all the pathologic glands studied, it was possible to make the diagnosis quite as accurately from the examination of sections fixed in Zenker's fluid and stained with hematoxylin and eosin as it was by studying the mitochondrial preparations. For routine work, a study of the amount of parenchyma, character of the stroma, size of the cells, character of the colloid and amount of vacuoles in the colloid is believed to be of more value than is a study of the mitochondria of the gland. Furthermore, it is difficult to obtain good mitochondrial stains in many pathologic thyroids, and poor preparations are apt to be misleading. Unfortunately, none of the unusual exophthalmic goiters which, histologically, resemble the normal adult thyroid were encountered in this series. A cytologic study of a gland of this type would be extremely interesting.

CONCLUSIONS

1. Chromophil granules and chromophobe vacuoles can be demonstrated in the cells of normal and pathologic thyroids.

2. It is believed that these are the secretion antecedents, and that the colloid is a mixture of the two.

3. The chromophil granules vary independently of the activity of the gland, and do not contain the active principle of the thyroid.

4. The chromophobe vacuoles vary directly with the activity of the gland, and contain the active principle of the thyroid.

5. No abnormal secretory antecedents were demonstrable in either toxic adenomas or exophthalmic goiters.

6. All hyperactive glands examined contained an excess of the normal chromophobe secretion.

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42. Giordano, A. S., and Caylor, H. D.: Histological Study of the Effect of Ligation of the Thyroid Vessels in Exophthalmic Goiter, Surg., Gynec. & Obst. **36**:75 (Jan.) 1923.

7. The mitochondria were present in the living cells of all glands studied, and were increased in the cells of all hyperactive glands.

8. The secretory antecedents do not arise directly from the mitochondria.

9. Mitochondria probably have some function in connection with the general metabolism of protoplasm, and are not responsible for the specific activities of the cells that contain them.

A REVIEW OF UROLOGIC SURGERY

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NEPHRITIS

Rovsing [25] reports 157 cases of nephritis treated surgically by himself and other Danish surgeons over a period of thirteen years. These cases are divided into four groups:

1. Interstitial nephritis and perinephritis are associated with paroxysmal attacks of hematuria and pain, and no albuminuria is present in the intervals. Macroscopically, perinephritis fibrosa, with more or less adhesive growth of the membrana propria to the sclerosed fatty capsule, is found. Anatomically, interstitial nephritis is found. These cases are at times associated with a uric acid or oxalate diathesis; they are forerunners of those in Group 2.

2. Interstitial and usually granular nephritis and perinephritis with hematuria, pain and constant albuminuria. Often there is contracted kidney and high blood pressure in such cases.

3. Cases of diffuse parenchymatous nephritis (tubular nephritis, chronic nephrosis). Two cases of this group were unilateral.

4. Glomerulonephritis. As a separate group are listed cases of orthostatic albuminuria.

The operative procedure carried out in most of the cases was nephrolysis, that is, shelling out the kidney from its fat and connective tissue capsule. In cases of severe hemorrhagic nephritis, in which nephrectomy is usually felt to be indicated, nephrolysis might be a better method. The operation is carried out through a lumbar incision; the kidney is stripped from its fatty capsule; the membrana propria is lifted up and incised near the convexity of the kidney and stripped off by means of blunt dissection to the renal hilum. A cigaret drain is

25. Rovsing, T.: Chirurgische Behandlung der Nephritiden, Ztschr. f. urol. Chir. **15**:210-211, 1924.

left in the wound. Modern serum drainage for a few days and healing without complication result, as a rule. If the patient's condition permits, a small bit of the renal parenchyma is removed at the time of operation for microscopic examination. A local anesthetic may be used for the operation. The end-results showed healing and improvement in each group: Group 1, 98.3 per cent.; Group 2, 80.3 per cent.; Group 3, 70.3 per cent., and Group 4, 88.2 per cent. Six patients with orthostatic albuminuria were dismissed as cured. On subsequent investigation it was found that eleven patients died from their renal disease, while eight succumbed to other maladies. Three patients died as the result of operation. Cessation of hematuria, disappearance of edema and fall of blood pressure were frequently striking. When the period of observation (thirteen years) is considered, the results were astonishingly good.

[ED. NOTE.—This report is thorough and the end-results reported are unusual. It should prove a stimulus to surgeons in this and other countries to proceed with renal decapsulation or nephrolysis in certain types of nephritis which do not respond to medical treatment after a reasonable period of trial. The operation is simple, can be carried out with little danger, and the end-results reported by so cautious and conservative an investigator as Rovsing show that the procedure may frequently be of definite and permanent value in a group of cases in which the prognosis might otherwise be very dubious.]

Pillet [26] reported a case of repeated hematuria of three months' duration. Investigation showed that the bleeding came from the right kidney while the left functioned normally. At operation the right kidney appeared normal. Following decortication nephropexy was performed. Permanent cure followed. Pillet discusses the question of whether in unilateral bleeding with an apparently normal kidney at operation, nephrectomy or decapsulation should be performed. Against nephrectomy is the argument that it may be questioned whether the disease is one-sided. The other kidney may bleed also from time to time and yet at examination appear normal. The factors may compel the operator to perform a nephrectomy: the bleeding may be so severe as to threaten life, or there may be a small tumor in a kidney which appears normal. If the patient's condition is such as to make exploratory nephrotomy hazardous, nephrectomy may be advisable.

Quinby's [27] report of the effects of decapsulation of the kidney in nephritis, as observed in the wards of the Peter Bent Brigham Hospital, are timely because of the persistence of reports in the literature of the

26. Pillet: Néphrite hémorragique; Décortication; Néphropexie; Guerison, J. d'urol. **16**:495-496, 1923.

27. Quinby, W. C.: A Note on the Results of Decapsulation of the Kidney for Various Forms of Nephritis, J. Urol. **13**:321-324 (March) 1925.

beneficial action of this operation. Quinby finds that the feeling is still prevalent that in some forms of nephritis this operation should be advised because of the supposed increase in, or moderation of, the vascular supply of the organ which may follow. Three cases are reported: one a case of hemorrhagic nephritis, one of acute tubular nephritis from mercuric chlorid poisoning, and one of chronic glomerulonephritis with edema. After bilateral decapsulation these cases were observed carefully with respect to the chemistry of the blood, as well as other more general observations, and in none of them was there demonstrated any benefit whatever, even of a temporary character. The patient with mercuric chlorid poisoning died at about the expected time, namely, five days after onset; the other two are still under observation, their course since operation apparently uninfluenced by this procedure.

POLYCYSTIC KIDNEY

Harttung [28] reports that the mortality of nephrectomy for polycystic kidney is 30 per cent., and of nephrotomy 45 per cent. The poor results of nephrotomy are due to bleeding, infection and postoperative fistulas. If the diagnosis of cystic kidneys is established and one kidney is functionless and the other has good function, then nephrectomy on the side most diseased is regarded as the method of choice. If one pole of the kidney is diseased and the remaining portion of the kidney is free from cysts, resection of the diseased pole may be considered. This, however, has the inherent dangers of nephrotomy. Operative procedures of any kind are contraindicated unless there is pain, bleeding or infection in the kidney chiefly involved and the remaining kidney is relatively free. The procedure of Payr who punctures the multiple cysts with a galvanocautery, thus reducing the size of the kidney, has yielded some good results, and Harttung feels that in some cases this procedure may be better than either nephrectomy or nephrotomy.

[Ed. Note.—Nephrotomy and multiple puncture in cases of polycystic kidney have not proved satisfactory. If there is definite involvement of both kidneys, as is usually the case when the situation demands surgical intervention, these procedures at best seem to be measures of desperation, which offer little in the way of permanent benefit to the patient. Cystic disease, after its development begins to be so widespread as to interfere with renal function, is progressive and, as Harttung shows, any palliative procedures that attempt to remove multiple cysts leave the kidney in a state in which recovery of any considerable part of its former function is very questionable. If nephrotomy or any

28. Harttung, H.: Zur Anzeigestellung für die operative Behandlung der Cystenniere, Ztschr. f. urol. Chir. **15**:200-211 (March) 1924.

of the puncture operations is carried out, it is very essential not to destroy the remaining renal parenchyma; meticulous care and gentleness must be used. The kidney should not be delivered, and extensive attempts to strip the capsule are not advisable. Polycystic kidneys after rupture of some of the large cysts have a tendency to bleed freely, even with fatal results.]

Young [29] reports five cases of polycystic disease of the kidneys. In one case the right kidney, which was enlarged, was removed; the patient died from uremia on the thirteenth day. In a second case of nephrectomy for hemorrhage, the patient was alive and in comparatively good health two years after operation. In the third case several large cysts were evacuated after surgical exposure of the kidney; the patient recovered from the operation, but it was necessary to pack the drained area in the kidney. In the fourth case nephrectomy was performed. Seven months later the patient was still alive but was uremic, and the opposite kidney seemed to be increasing in size. In the fifth case both kidneys were distinctly enlarged; nothing surgical was done.

[ED. NOTE.—In a number of cases at the Mayo Clinic, nephrectomy was performed for polycystic kidneys with comparatively good results. Some of the patients are alive and fairly well from five to eight years after operation. Even though several cases have been reported as unilateral polycystic disease, the condition is practically always bilateral. The involvement is rarely the same in both kidneys, one usually being much larger than the other. Generally following nephrectomy the remaining kidney gradually increases in size, although it is impossible to know definitely that this increase is due primarily to the removal of the other. Stripping the capsule or puncturing the cysts is an operation carrying a high risk and should only be performed under exceptional circumstances, such as encroachment on other organs, obstruction or severe pain.]

RENAL INJURY

Opokin [30] reviewed 211 cases of gunshot wound of the kidney observed during the World War. Gorasch estimates that they compose 0.14 per cent. of all gunshot wounds, while Steinfield estimates that they amount to 0.35 per cent. Tearing, cleaving wounds are more common than sharp, clean wounds. If the projectile has traversed the pelvis of the kidney, then the vessels are likely to be injured. Sudden death may occur if injury to the vessels is great. Complete destruction of the kidney is observed with shrapnel wounds.

29. Young, R. F.: Polycystic Disease of the Kidneys, Brit. J. Surg. **12**:244-253 (Oct.) 1924.

30. Opokin, A.: Ueber Schussverletzungen der Nieren nach dem Material des Weltkrieges, Urologija **1**:13-16, 1923.

Perirenal hematoma is frequently observed, and often pieces of renal parenchyma lie therein. Kidney wounds are frequently accompanied by wounds of other organs in the peritoneal cavity or in the chest. Blood in the urine is a frequent symptom, and may last from a few hours to weeks or longer, if a vessel is injured. Profuse hemorrhage is an indication for immediate operation. Urinary fistula means injury of the pelvis or ureter. If infection sets in, local inflammatory reaction with painful swelling in the lumbar region, often extending to the anterior abdominal wall, is found. Cystoscopy is an aid to diagnosis; the finding of coagulated blood in the bladder or blood coming from the ureter of the injured side is important. Conservative or expectant treatment suffices in the less severe cases and, according to the statistics of some observers, gives better results than operative treatment. However, the danger of spreading infection is greater under such circumstances. Of the operative procedures, primary nephrectomy is indicated in cases of extensive wounds that involve the hilum or blood vessels or destruction of the ureter. Nephrectomy is preferable to renal suture or tamponade with living tissues, as almost invariably infection will take place if the latter procedures are carried out. Secondary nephrectomy is indicated by infection or persistent bleeding in cases of urinary infiltration or fistulas, and also when there is extensive formation of scar in the renal capsule or parenchyma. The mortality varies with the involvement of other organs. When the kidney alone is injured the mortality is about 25 per cent.

[Ed. Note.—It is remarkable that so little has been written of renal injuries during the war. Statistical information in urologic literature in America has been very scant. This contribution from a Russian source is interesting and is consistent with our rationale of the treatment of renal trauma such as is seen in the accidents of civil life. The argument for conservative or expectant treatment in the early stages is good, but with the development of shock, hemorrhage of a persistent character or infection operation should not be delayed.]

RENAL NECROSIS

Falci [31] states that total necrosis of the kidney due to renal infarct is practically always associated with either a cardiac or a vascular disorder. The symptoms are not always definite, but onset of pain in the renal area is usually sudden and violent. Albuminuria is common and appears suddenly and in large amounts. The prognosis concerning patients who are not operated on is very poor; 85.3 per cent. died. Nephrectomy is the operation of choice; only two patients (9.09 per cent.) died following nephrectomy.

31. Falci, Emilio: Sur la nécrose du rein, J. d'urol. **18**:449-465, 1924.

TECHNIC OF URETERAL OPERATIONS

Beer and Hahn [32] describe methods of removing stones in the ureters by means of ureteral catheters. They pass a catheter beyond the stone and allow it to remain in place from two to five days; in some cases removal of the catheter is followed by the passage of the stone. A single treatment usually suffices to deliver the stone, which is passed with very little pain. This method was tried in the Mount Sinai Hospital in twenty-seven cases; it was successful in ten. In twenty-two cases in which this method was definitely indicated, there were ten proved successes. The indwelling catheter, besides effecting the passage of ureteral stones, also usually drains the kidney and relieves it of back pressure and infection. The usefulness of the indwelling catheter is emphasized by comparing recent results with the results obtained before the adoption of this method. In a series of 114 cases diagnosed as ureteral stones, stones were passed during or following cystoscopic manipulation in twenty-three. In this series of 114 cases, which were observed before the indwelling catheter was in use, seventy-six were favorable, and in twenty-three (30 per cent.) stones passed following one or more cystoscopic manipulations. Thus, there is a definite gain of from 50 to 100 per cent. by the use of the indwelling catheter over the other cystoscopic methods used. It should be understood that this method is useful only for the smaller or medium sized stones, particularly those in the lower half of the ureter. Beer and Hahn believe that this method is harmless, and if used intelligently will lead to the comparatively painless passage of many more ureteral stones following the first manipulation than would otherwise pass.

URETERAL CATHETERIZATION

Fullerton [33] advises the bilateral iliac incision and catheterization by making an incision in the ureteral wall in cases in which it is impossible to catheterize the ureters cystoscopically. He reports one case so treated. He also refers to another case in which the ureteral orifices could not be found, even when the bladder was opened. In this case, by stripping back the peritoneum, he found where the ureters entered the bladder and so located the orifices and catheterized the ureters.

[ED. NOTE.—It seems that such a radical procedure should be rarely if ever necessary. It is unusual to find a patient whose ureters cannot be catheterized through the cystoscope, and yet whose general condition is good enough to justify a general anesthetic and a major operation in order to make or confirm a diagnosis.]

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32. Beer, Edwin; and Hahn, L. J.: Use of Indwelling Catheter to Induce Passage of Ureteral Stones, J. A. M. A. **84**:1028-1029, 1925.

33. Fullerton, Andrew: Retroperitoneal Catheterization of the Ureters, Brit. J. Surg. **12**:351-354 (Oct.) 1924.

URETERAL ANASTOMOSIS

Krogius [34] discusses a technic of ureterovesical anastomosis in which the terminal end of the ureter is dissected free so that its lower portion may be attached laterally to the wall of the bladder on its outer side. An incision through the serosa and outer muscle layers of the lateral wall of the bladder is made, and two tongue-shaped lappets dissected back. The length of this incision is from 3 to 4 cm. After catheterization of the bladder, an incision is made into its cavity, about 1.5 cm. long. The lower portion of the loosened ureter is placed in this cavity, a split having been made in its lateral wall. The cut ureteral and bladder walls are sutured together so as to make the anastomosis below the deeper muscle layers. The two tonguelike lappets are sutured down over the ureter and the wall of the bladder, and serve as a covering for the anastomosis. Drainage may be placed down to the site of suture. Krogius operated successfully in a case in which stricture of the ureter resulted from an old stone.

URETEROSTOMY

Duvergey [35] believes that in ureterostomy the ureter should be transplanted to the iliac region, as this permits a large curve, reduces the chance of ureteral occlusion, and also facilitates the care of the opening. The two cutaneous openings should be symmetrically placed and just a little in front of the anterior superior iliac spines. The apparatus for collecting the urine then rests on soft tissue rather than on the pelvic bone. The ureter should be exposed through an incision in the iliac region, 2 cm. anterior to the iliac spine; the aponeurosis of the external oblique muscle is cut, and the muscle fibers divided. The peritoneal fold is drawn toward the middle line. The ureter is pulled up to the surface of the skin, care being taken to prevent kinking or pressure on the ureteral walls. A small tube is placed in the opening of the ureter; the ureter above the skin dries up and the ureteral wall adheres to the edge of the skin. In ten cases there were two postoperative deaths. Most of these operations were performed for cancer of the bladder. Usually the hemorrhage, pollakiuria and vesical tenesmus disappeared. It is necessary to prevent stenosis of the orifice by dilation. An ascending infection may occur; it is favored by a stenosis of the ureteral outlet. The operation is suitable for inoperable carcinomas of the bladder, severe

34. Krogius, Ali: Laterale Uretero-Cystoanastomose mit plastischer Überdeckung der Anastomosenstelle als Behandlungsmethode bei Strikturen des unteren Ureterendes, Zentralbl. f. Chir. **51**:92-94 (Jan. 19) 1924; abstr., Ztschr. f. urol. Chir. **15**:305-306, 1923-1924.

35. Duvergey: De l'uréterostomie iliaque bilatérale définetive, Arch. franco-belges de chir. **32**:541-544 (June) 1924.

vesical tuberculosis, and for the uterine carcinomas which have invaded the bladder. Suprapubic cystostomy does not divert the urinary flow, and is more difficult to take care of. Bilateral nephrostomy is a long, tedious, difficult operation. Implantation of the ureters into the intestine has a high mortality, and is usually associated with pyelonephritis.

URETERAL OBSTRUCTION

Strassmann [36] found that pregnant women not infrequently have moderate pyelonephritis and dilatation of the renal pelvis without marked localizing symptoms. The pressure on the ureters by the pregnant uterus causes urinary stagnation in the renal pelvis. This associated with a mild chronic urinary infection, marked constipation, or acute infection in other parts of the body, may institute severe pyelonephritis. Strassmann, on this account, advises preventive measures in pregnant women, especially those who have moderate renal discomfort. Respiratory infections are to be avoided, the bowels should be kept open, and a diet prescribed comparatively free from proteins and substances injurious to the kidneys.

[ED. NOTE.—Strassmann reported six cases, in five of which obstruction was on the right. In large series of cases it will be found that the right side is involved in even a larger proportion, owing primarily to the fact that the uterus rotates slightly but definitely toward the right side. Pregnancy increases this rotation, causing pressure on the right ureter. In mild cases of renal pain, infection and pelvic obstruction, alkalis, as advised by Kidd, are indicated and give the best results. Doses of 60 grains (3.8 gm.) of sodium bicarbonate and 20 grains (1.3 gm.) of potassium citrate are given by mouth at two-hour intervals for several days. In a number of cases in which catheter drainage of the renal pelvis and lavage with mild antiseptic solution caused no change in the symptoms, relief was obtained immediately by alkalis.]

HYDRO-URETER AND HYDRONEPHROSIS

Young [37] reports two cases of extensive prolapse of the pelvic organs with associated bilateral hydro-ureter and hydronephrosis. The first case was that of a cadaver in which there was extensive prolapse, the bladder being pulled down with the uterus and other pelvic organs. Both ureters and the renal pelvis were enormously distended. There was considerable urine in the bladder, and on squeezing it a fluid wave was transmitted up to the renal pelvis. The second patient was a

36. Strassmann, P.: Zur Harnleiterverlegung ("Ureter-Kompression") bei Schwangeren, Ztschr. f. Urol. **18**:620-625, 1924.

37. Young, J.: Hydroureter and Hydronephrosis Secondary to Prolapse and Cystocele, Tr. Edinburgh Obst. Soc. **83**:207-211, 1923-1924.

woman, aged 52, with a history of having had prolapse for sixteen years; there had also been frequency of micturition for three years. There was complete procidentia, which was irreducible. This patient was operated on, and later came to postmortem. The kidneys were small and hydronephrotic, and the ureters slightly dilated. Young says that Brettauer and Rubin [38] found eight cases of hydronephrosis in ten cases of prolapse. In the two cases in which there was no hydronephrosis, prolapse was incomplete. Tandler and Halban report fifteen cases of dilated ureter in twenty-three cases of prolapse, but make no reference to the condition of the kidneys. The dilatation is probably due to a kinking of the ureter over the pulled down uterine vessels. This view is supported by the findings of Tandler and Halban in which the portion of the ureter below the uterine vessels was not found dilated.

TECHNIC OF VESICAL OPERATIONS

Papin [39] advises frequent changes of the drainage tubes or Pezzer catheters in cases of cystostomy, especially when fistulas must be kept open for a certain length of time. The bladder should be irrigated through the drainage tube or through the urethra (by catheter) with silver nitrate or boric acid solution. The edges of the wound may need cauterization from time to time. If stricture of the fistulous tract ensues, one may employ sounds, bougies, laminaria or the Kollman dilator. The drain should be long enough to reach the bladder and ensure evacuation, but should not be so long as to cause pain. To control bleeding, irrigation with 5 per cent. antipyrin solution, the administration daily of 4 gm. of calcium chlorid, or cauterization of the bleeding granulations is recommended.

LESIONS OF THE URETHRA

Braasch [40] states that the cystoscopic data which have proved most valuable in the recognition of lesions of the nerves of the urinary tract are: trabeculation of the bladder, relaxation of the urinary sphincter and prostatic urethra, and diminished sensation. Braasch divides these lesions into those in which there is clinical evidence of involvement of the central nervous system, and those in which such involvement is not evident, the lesion apparently involving only the terminal nerve supply of the bladder. The cystoscopic picture of the

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38. Brettauer, Joseph; and Rubin, J. C.: Hydro-ureter and Hydronephrosis; a Frequent Secondary Finding in Cases of Prolapse of the Uterus and Bladder, Am. J. Obst. & Gynec. **6**:696-709 (Dec.) 1923.

39. Papin, E.: De la conduite à tenir chez un malade cystostomisé, J. d. practiciens **38**:137-139, 1924; abstr., Ztschr. f. urol. Chir. **16**:44-45, 1924.

40. Braasch, W. F.: Data with Regard to Lesions of the Nerves of the Urinary Tract, J. Urol. **13**:383-398, 1925.

first type is marked relaxation of the internal sphincter and prostatic urethra, ridgelike trabeculations, and diminution in sensation in the urethra and bladder. The degree of relaxation of the sphincter may vary from a barely perceptible dilatation of the internal sphincter to relaxation of both sphincters and prostatic urethra. The trabeculation may vary from a state in which the condition is scarcely perceptible to one in which the trabeculae stand out like elevated ridges, with deep cellules between. Likewise, sensation in the prostatic urethra and bladder may be such that scarcely any change is perceptible, or there may be such complete absence of sensation that the patient will not be conscious of instrumentation in the urethra or bladder. Trabeculae occurring with this type appear through the cystoscope as fine, thin elevations extending across the bladder in ridges which often predominate in the upper half of the bladder. In contrast, trabeculae observed in cases of mechanical obstruction are of a coarser type, and are more often predominant in the lower portion of the bladder.

Urinary control in this type of bladder varies largely with the degree of relaxation of the sphincters. In the male patient, the degree of urinary incontinence varies with the degree of relaxation in the external sphincter and prostatic urethra. There may be wide relaxation of the internal sphincter without incontinence so long as the external sphincter remains intact. Occasionally relaxation of the external sphincter also is noted with little or no incontinence. In the female, evidence of relaxation of the sphincter does not have the same diagnostic importance as in the male. Relaxation of the sphincter, causing a slight degree of incontinence, may result from cicatricial changes in the urethra, injury to the sphincter, injury to the terminal nerve supplying the sphincter, or from relaxation of the muscular support in the perineum and vaginal walls. With a typical cord bladder there is such a marked diminution of sensation in the prostatic urethra that the patient is unaware of the cystoscope as it is introduced.

The classical cystoscopic evidence of cord bladder, sphincter relaxation, trabeculation and sensory disturbances are best seen in tabes dorsalis. In these cases the amount of residual urine varies inversely with the degree of sphincter and detrusor relaxation, the amounts being largest when the sphincter and sensory disturbances are not marked. Arteriosclerosis also is a common disease affecting the cord centers and changing the cystoscopic picture. The most common finding with this lesion is a variable amount of residual urine together with slight trabeculation. Spina bifida cystica is often the very evident cause of widespread disturbance of innervation of the bladder, rectum and lower extremities. The cystoscopic picture of spina bifida occulta varies with the degree of the nerve lesion and secondary infection. With mild lesions there is usually a spastic condition of the prostatic urethra and

no definite sphincter relaxation. With widespread and late lesions, relaxation of the sphincters and prostatic urethra is frequently observed in male patients.

The second type of lesion in which there is evidence of paralysis of the motor nerves controlling the bladder, but not of definite diseases of the nerve centers, is exemplified in the so-called atonic bladder. There are two types of atonic bladder: those in which there is motor disturbance alone, and those in which there is both motor and sensory disturbance. On cystoscopic examination the findings are usually quite different from those observed with the more common cord bladder. The bladder musculature appears to be flabby, with complete lack of tone. Bladder trabeculations are not usually so marked as in the tabetic bladder, and may be absent. Dilatation of the sphincter, when present, is but slight. There may be no diminution in sensation either in the prostatic urethra or bladder, although in some cases there is definite diminution. The expulsive power of the bladder is greatly diminished or entirely absent. Disturbance of bladder control, marked by varying degrees of incontinence, is much more common in the female than in the male.

Braasch states that the cystoscopic findings in cases of lesions of the central nervous system are of the greatest diagnostic value, and if there is any doubt with regard to the existence of such a lesion, or of the involvement of the urinary tract with a proved lesion, cystoscopic examination should be made. In the course of routine cystoscopy, considerable variation will be noted in the data resulting from the different types of nerve lesions, many of which may be recognized as pathognomonic.

PARALYSIS OF THE BLADDER

Bugbee [41] reports the case of a boy, aged 1 year, who was admitted to the hospital with acute retention of urine of twenty-four hours' duration. On admission the parents said that the abdomen had been distended for twenty-four hours, that thirty-six hours previously the child became restless, and had been crying most of the time since. His diapers had been wet slightly for the greater part of the time; he apparently urinated in small quantities at frequent intervals. An enema had given only slight relief. The examination was negative aside from marked protrusion of the lower abdomen. The temperature was normal; the throat culture was negative; the tuberculin reactions were negative; there was no paralysis of the muscles of the extremities. A catheter was passed and 135 c.c. of urine removed, diminishing the size of the abdominal tumor; not all the urine was withdrawn. The urine was acid, contained a trace of albumin and a few hyaline casts, but

41. Bugbee, H. C.: Paralysis of the Bladder with Acute Poliomyelitis, J. Urol. 13:333-335 (March) 1925.

no sugar. Six hours later, 210 c.c. of urine was withdrawn, and the following day the child could not be catheterized. The bladder was 3.75 cm. above the navel and extremely hard. The child was in pain. Examination at this time showed a right foot drop, although the child could move the thighs and legs. The leukocytes numbered 13,600; polymorphonuclears, 51; lymphocytes, 42; mononuclears, 3; transitionals, 4, and eosinophils, 1. Six cubic centimeters of spinal fluid was withdrawn; this was cloudy, showed globulin 2 + and contained 220 cells. A diagnosis was made of acute poliomyelitis with paralysis of the bladder. During the next three days the bladder became more and more distended, seeming to fill most of the abdominal cavity. The child became progressively weaker; the paralysis extended to the extensor groups in both lower extremities, resulting in doubtful foot drop; the temperature rose steadily. An anesthetic was administered and a cystoscopic examination made. No obstruction was found at the vesical neck; there was a protrusion of the posterior wall of the bladder. The following day a suprapubic cystotomy was performed; this revealed a very large, completely paralyzed bladder which was folded over on itself, the posterior wall being thickly covered with adherent pus and mucus. Following the suprapubic drainage, the patient improved rapidly. The bladder has been irrigated through the suprapubic tube, which has been changed from time to time; the suprapubic tube has also been clamped off for a few hours at a time, but the child has passed only small amounts of urine on a few occasions through the urethra.

VESICAL TUMORS

Malavasos [42] recommends electrocoagulation as a preoperative procedure to reduce the size of the tumor in cases of extensive papillomatous growths with wide base and infiltration of the wall of the bladder. Recurrence in the operative scar suggests malignancy. Small recurrent papillomas in the mucosa of the bladder as a rule are benign and will yield to electrocoagulation. The patient should return every two or three months to be examined for recurrent growths, and if found they should be treated with electrocoagulation.

[ED. NOTE.—It is fast becoming the practice in urologic clinics the world over to insist that patients with tumors of the bladder should come back at short intervals for examination. In this way the effect of various forms of treatment and the end-results will be checked so that, as the years go by, more effective measures will be employed in the treatment of this type of tumor.]

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42. Malavasos, A.: Zur Behandlung der Papillomrezidive, Ztschr. f. urol. Chir **16**:1-10, 1924.

VESICAL DIVERTICULUM

Negro and Blanc [43] report thirteen cases of diverticulum of the bladder from Marion's service; in seven the orifice of the diverticulum was in the ureteral area, in three in the upper lateral region, in two in the fundus, and in one in the urachal area. In eight cases the diverticulum was single, and in five, multiple. Diverticula are most common after the age of 40 years. Three patients in this series were less than 40. Two were women. The multiplicity usually varies inversely with the size of the diverticula. Divided micturition is a suggestive symptom, but is not common. Palliative treatment is generally insufficient and in most cases operation is indicated. In most cases resection should be carried out, although in an occasional case, particularly one of the fundus, the neck of the diverticulum may be dilated.

[ED. NOTE.—The orifices of either a single diverticulum or multiple diverticula are usually in the region of the ureteral orifices. Of 163 cases compiled by Hinman, 123 (75.4 per cent.) were near the ureteral orifices. The opening is sometimes found on the lateral wall or in the fundus. Only rarely is the trigon involved, although occasionally an opening is found just above the interureteric ridge. Diverticula which open in the dome are generally small and may be multiple. True single, large diverticula occurring in the dome are rare and are sometimes confused with cystic conditions of the urachus. In some cases the ureter opens directly into the diverticulum or it may be incorporated in the wall of the sac, or matted in adhesions, so that it must be cut in order to remove the diverticulum. Hinman found the ureter affected in twelve of 205 cases noted in the literature. Marion described a case in which both ureteral orifices were contained in a diverticulum. In cases in which the ureteral opening is found to be marginal, the adjoining mucous membrane should be turned into the closure of the bladder after resection of a diverticulum.]

Wolfson [44] reports a case of diverticulum in the bladder which interfered with labor. In traction the obstetrician encountered obstruction; this was suddenly overcome with a jerk, and the child was then delivered readily. Several months later the diverticulum, which was deeply placed beneath the bladder, was removed by finger traction. The diverticulum had a capacity of 75 c.c.; in removing the sac the left broad ligament was sacrificed. The wound was closed and had healed com-

43. Negro, M., and Blanc, H.: Considérations cliniques et opératoires au sujet de treize cas de diverticules vesicaux, J. d'urol. **18**:217-247 (Sept.) 1924.

44. Wolfson, W. L.: Diverticulum of the Bladder Causing Dystocia at Labor, Surg., Gynec. & Obst. **40**:524-527, 1925.

pletely four weeks after the operation. Six weeks after the operation, the patient had excellent control of the bladder and the urine was free from pus.

Duvergey [45] removed a diverticulum from a bladder by the combined intravesical and extravesical method. The mucous membrane was excised at the neck of the diverticulum and the sac removed extravesically. Prostatectomy was then performed.

[ED. NOTE.—A recent report from the Mayo Clinic gave statistics concerning thirty-seven cases of excision of the diverticulum and prostatectomy; three patients died, a mortality of 8.1 per cent. In thirty-one cases the diverticulum was excised extravesically; in six it was removed transvesically. In twenty-three cases complete data were obtainable; following operation fifteen patients (65.1 per cent.) are still living; twelve are completely cured from one to nine years after operation.]

SIGMOIDAL AND VESICAL DIVERTICULITIS

Colby [46] reports two cases of diverticulitis of the sigmoid involving the bladder. In one case a preliminary colostomy was performed, and later the sigmoid was separated from the bladder and the openings were closed. The colostomy was closed two weeks later. In the second case the bowel and bladder were disconnected, but the symptoms recurred. Later a cecostomy was performed; the diseased segment of the sigmoid was resected, and an end-to-end anastomosis performed. The results were excellent in both cases.

VESICAL STONE

Desvigne [47] removed a stone from the bladder of a man, aged 46. The calculus had formed around a piece of shrapnel which had entered the bladder nine years before.

[ED. NOTE.—The formation of foreign bodies in the bladder is not uncommon. Usually articles inserted into the bladder through the urethra are incrusted with calculi. Cases in which the foreign body enters the bladder through an incised or contused wound are unusual. In one case in the Mayo Clinic, a stone formed around a fragment of

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45. Duvergey: Diverticule de la vessie avec adénome prostatique traité et guéri par la diverticulectomie et la prostatectomie, J. d'urol. **18**:525, 1924.

46. Colby, F. H.: Bladder Involvement in Diverticulitis of the Sigmoid, Boston M. & S. J. **192**:4-8 (Jan. 1) 1925.

47. Desvigne: Calcul de la vessie développé autour d'une balle de shrapnell, ayant séjourne 9 ans dans la vessie; Lithotritie et taille hypogastrique secondaire, J. d'urol. **18**:526, 1924.

knife blade; the patient had been stabbed several years previously, and the blade had gradually worked into the bladder.]

VESICAL ULCERS

Rubritius [48] reports five cases of incrusted ulcer of the bladder. This condition, first described by Fenwick and Zuckerkandl, may occur as a small clear-cut ulcer or as multiple or diffuse ulcerated areas, usually in the region of the ureteral orifice. They are frequently associated with renal infection and do not yield readily to conservative treatment. In most cases it is necessary to excise completely the area of the bladder containing the ulcer; this may include the lower end of the ureter. The condition is not uncommonly associated with pregnancy.

[ED. NOTE.—This is the so-called simple ulcer of the bladder and is decidedly different from the submucous (Hunner) type of ulcer, concerning which a number of articles have been written. The treatment, partial resection of the bladder, is the same in both cases. The incrusted ulcer, especially the diffuse or disseminated type, is practically the same condition, usually termed in this country alkaline phosphatic cystitis. In several of the cases reported by Rubritius small phosphatic calculi were passed; the urine was alkaline and bacteria similar to those found in alkaline phosphatic cystitis cases were present.]

VESICAL HERNIA

Laskownicki [49] noted twenty-three cases of strangulated hernia of the bladder in the literature. In sixteen the strangulation occurred in the inguinal canal, and in seven in the femoral canal. He reports a case of strangulation in the femoral canal. The bladder was opened during the course of the operation and closed in two layers. There had been no symptoms of bladder trouble; digestive disturbances, abdominal colic, distention, nausea, vomiting and an acceleration of the pulse rate all suggested strangulation of the intestine. The diagnosis of bladder involvement was not made in any of seven cases of femoral strangulation. In four it was made during the course of the operation; the bladder was opened in nine cases. In three cases the diagnosis was made after the operation. In some cases the diagnosis may be made by the spasmodic colic over the bladder which radiates toward the pubes, the urethra or the thigh. There may be vesical tenesmus, retention or mild hematuria. In some cases a catheter introduced into the bladder may be felt in the hernial sac.

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48. Rubritius, H.: Das inkrustierte Geschwür an den Harnleitermündungen, Ztschr. f. Urol. **18**:537-544, 1924.

49. Laskownicki, S.: Un cas rare d'incarcération de la vessie dans l'anneau crurol, J. d'urol. **18**:251-253, 1924.

EMBRYONIC RESTS

Colby [50] reports a case in which there was a small tumor in the base of the bladder. The bladder was explored through a median suprapubic incision, and the tumor area excised. Histologic examination revealed glandlike structures lined with columnar epithelium, chiefly of the goblet cell type. These mucus secreting cells bear a resemblance to rectal mucosa. Similar areas of gland formation are found in the mucous membrane of exstrophied bladders. Colby believes that the condition in this case, in which the section was found to be composed of groups of mucus secreting cells like those of the rectum, was similar to that of the glands of exstrophied bladders.

[ED. NOTE.—Vrolike was the first to remark on the curious mucous covering of exstrophied bladders. Ehrlich explains the presence of the glandular covering from an embryologic standpoint. The bladder and intestines both come from the same source; owing to its unusual situation, the bladder has not the stimulation to change over to the usual type of transitional epithelium, but retains that of the intestines. Enderlen thinks that the glandular formation occurs in response to a certain stimulus developing after birth. The normal bladder contains small glandular areas, well described by von Brunn and later by von Limbeck. Stoerck and Zuckerkandl describe a glandular cystitis which developed into malignancy as a result of constant irritation.]

PREURETHRAL OPERATIONS FOR PROSTATIC OBSTRUCTION

Walker [51] reviews the factors leading to success in suprapubic prostatectomy. This success, however, is not so uniform among general surgeons as it is among those who specialize in genito-urinary surgery. In the London General Hospital for the years from 1914 to 1923, the mortality rate of prostatectomy for benign enlargement of the prostate was 22 per cent. Among genito-urinary specialists, Walker finds the immediate mortality somewhat over 5 per cent. Because of such mortality he feels that in suitable cases of prostatic obstruction, conservative treatment by urethra is indicated. The usual criticism of any such procedure is that it is not always successful, and that when successful the relief is frequently only temporary. These objections are overcome by a better selection of cases and improved technic. The third objection is that a certain proportion, generally placed at about 15 per cent., of apparently benign enlargements of the prostate show malignant changes and that any palliative operation fails to remove

50. Colby, F. H.: Embryonic Rests of the Urinary Bladder, Surg., Gynec. & Obst. **40**:528-545, 1925.

51. Walker, K. M.: Preurethral Operations for Prostatic Obstruction, Brit. M. J. **1**:201-204, 1924.

these malignant processes. Walker argues that even total prostatectomy will in many instances fail to remove completely such cancerous tissue and draws attention to the fact that, in two of the five cases of early malignant changes in apparently benign glands reported by Swan,[52] the disease later recurred. In view of these results, the argument of leaving malignant tissue may in many cases be disregarded.

Randall [53] is quoted as finding 33.5 per cent. of 158 enlarged prostates to be of the bar type, and so amenable to preurethral treatment. Walker has devised a diathermy punch which in external form resembles the Young punch, but the sheath is constructed of bakelite (an excellent insulating material allied to vulcanite) with a metallic lining. This lining comes to the surface only at the edge of the window situated below the beak; elsewhere it is insulated from the urethra by the bakelite covering. The punch is introduced with an obturator in position, and to facilitate its insertion in difficult cases a pliable bougie guide may be attached to the beak by means of a screw. When in position the obturator is withdrawn, and a system consisting of a telescope, a lamp, and inlet and outlet tubes for irrigation is substituted, thus converting the instrument into a posterior urethroscope. Under guidance of the eye the punch is now withdrawn until the bar is seen to engage the window. Once it is in position the instrument is held firmly and pressure exerted on the bar by slightly raising the proximal end. Connection is then made with the source of the diathermy current. Immediately the current is turned on, the inner metallic layer of the sheath becomes a urethral electrode, but owing to the insulation conferred by the bakelite covering the only point of contact with the urethra is the edge of the window engaging the bar. From this edge can be observed to spread a line of coagulation which within ten or fifteen seconds whitens the whole area of prostate engaged.

By maintaining continuous irrigation the process of diathermy can be carried out under complete ocular control, the current being turned off when it is judged that a sufficient depth of tissue has been destroyed. In order to remove the wedge of destroyed tissue and thus obtain immediate benefit without waiting for the separation of sloughs, the telescope and lighting system is withdrawn, and an inner tube, resembling that used in the Young punch, inserted. By inserting this and giving it, at the same time, a slight rotatory movement, a core of destroyed tissue about 2 cm. in length and 0.5 cm. in diameter may be removed.

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52. Swan, R. H. J.: The Incidence of Malignant Disease in the Apparently Benign Enlargement of the Prostate, Proc. Roy. Soc. Med. **16**:71-80 (Sect. Urol.) 1922-1923.

53. Randall, Alexander: The Varying Types of Prostatic Obstruction, J. Urol. **5**:287-308 (April) 1921.

This does not, however, constitute the whole amount of prostatic tissue destroyed by the operation, the full benefit of which will only be obtained at a later period when the sloughs have separated. The telescope and lighting system may then be reintroduced, the area of operation inspected, and a decision arrived at as to whether any further fulguration is required. If the operator is satisfied with the amount of tissue dealt with, the bladder is emptied, the obturator inserted, and the instrument withdrawn. In other cases Walker fulgurizes the bar obstruction through an indirect view cysto-urethroscope with satisfactory results.

THE RISKS OF PROSTATECTOMY

Walker,[54] in considering the risks of prostatectomy, reviews the results of operation and of catheterization. He quotes Squier's report that 50 per cent. of patients suffering from obstructing symptoms, without operative treatment, die within five years, even when catheterization is unnecessary; after catheterization is begun the average duration of life is two years and eight months. In view of this evidence, catheterization can only be a temporary measure. Freyer's reports on mortality are quoted showing that, whereas the mortality rate after prostatectomy in London hospitals was 21.5 per cent., his own figures during the same period were under 10 per cent. Similar figures are recorded coming from Whiteside, who reviewed 1,423 prostatectomies by thirty-four surgeons. The primary mortality in the patients attended by general surgeons was 26 per cent., whereas in those operated on by urologists it was 3 per cent. The two-stage operation, in cases of renal insufficiency, has done much to improve the result. The majority (about 69 per cent.) of the deaths following prostatectomy are due to trauma, hemorrhage, shock or sepsis. Preliminary drainage is considered the most satisfactory method of improving lowered renal function and reducing sepsis.

PROSTATIC TUMORS IN CHILDHOOD

Prostatic tumors in childhood occur rarely. Sysak[55] compiled twenty-two cases from the literature, four of small round cell sarcoma, six of myosarcoma, five of spindle cell sarcoma, one of adenosarcoma, and three of rhabdomyosarcoma. Sysak reports a tumor of the prostate in a child, aged 9 months, who died from disseminated tuberculosis. The tumor involved the right prostatic lobe, measured 66 by 40 mm., and was separated from the prostate by a broad, thick capsule of con-

54. Walker, K. M.: The Risks of Prostatectomy, Practitioner **112**:278-286 (May) 1924.

55. Sysak, Nikolaus: Ein Beitrag zu den Tumoren der Prostata im Kindesalter, Arch. f. path. Anat. u. Physiol. **247**:604-612, 1923.

nective tissue. The prostate itself seemed to be enlarged. The tumor tissue had extended into the prostate, infiltrated the wall of the bladder, and attacked the rectum. Histologically, the tumor consisted of sarcoma-like tissue with an outspoken plexiform character and undifferentiated supporting connective tissue. In one place the tumor took on a rhabdomyoplastic differentiation.

CYST OF THE PROSTATE

Thomson-Walker [56] reports the case of a prostatic cyst in a man, aged 46, who complained of difficulty in urination for two years. The onset was gradual, but the symptoms were severe for fourteen days. Micturition commenced freely, then suddenly stopped with a jerk, and this was followed by intense cramping pain and great straining, during which a small quantity of urine was passed in drops. Urinalysis was negative and the prostate was normal on recent examination, but there was 300 c.c. of residual urine. Cystoscopy revealed a cyst, about 2.5 cm. in diameter, attached to the anterior lip of the internal meatus. The cyst was incised with the high frequency cautery with complete, immediate relief of symptoms. Subsequent cystoscopy showed only a slight prominence on the anterior lip where the cyst had been.

TUBERCULOSIS OF THE PROSTATE

Scott [57] found only seven cases recorded in the literature which should be classified as primary tuberculosis of the prostate. To these seven cases, Scott adds an eighth. This patient was 83 years old, with an enlarged prostate and a slightly irregular epididymis on the left side. There was nothing about the prostate to suggest tuberculosis. After suitable preoperative treatment, the prostate was removed. The patient died a week later from pneumonia. On microscopic examination, in addition to true benign prostatic hypertrophy, typical tuberculous tissue was found. Necropsy revealed no other tuberculosis of the genito-urinary organs, the only other tuberculous lesions being inactive healed foci in the apexes of the lungs.

MALIGNANT DISEASE OF THE TESTIS

Handfield-Jones [58] states that the radical operation for malignant disease of the testis is unjustified. In support of this contention, he

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56. Thomson-Walker, John: Case of Cyst of the Prostate, Proc. Roy. Soc. Med. **17**:21-22 (Sect. Urol.) 1924.

57. Scott, W. W.: Tuberculosis of the Genito-Urinary Tract Confined to the Prostate, J. Urol. **12**:515-526 (Nov.) 1924.

58. Handfield-Jones, R. M.: The Treatment of Malignant Disease of the Testicle, Lancet **2**:850-852 (Oct. 25) 1924.

presents experiments of his own and those of Jamieson and Dobson in which distribution of the lymphatic drainage from the testis is shown. On the right side the glands primarily involved lie on the anterior surface of the inferior vena cava and in the groove between it and the aorta; and the dissection must extend from the level of the renal vein to the termination of the common iliac artery. On the left side the glands affected will lie to the left of, and on, the anterior surface of the aorta, and bear an intimate relationship to the origin of the inferior mesenteric artery, and the extent of the dissection is as wide as that on the right. Further, the spermatic vessels and the testicular lymphatics are firmly attached to the posterior surface of the peritoneum, and when the latter is pushed inward during the operation the vascular lymphatic chain has to be dissected off the peritoneum. In so doing there is considerable danger of rupturing the fragile lymphatics and in this way seeding the wound with malignant cells. Such extensive dissection as is necessary to remove these glands seems unjustified. He points out that generally the only good results shown in the surgical treatment of malignant disease are in early cases, that is, in cases without lymphatic involvement. Therefore, if the disease has advanced into the lymphatics, no attempt should be made at their removal, and if there is no lymphatic involvement, radical surgical intervention is unnecessary. He does not place much faith in roentgen-ray or radium therapy in these cases, but advises the simpler orchidectomy.

GONORRHEAL EPIDIDYMITIS

Chenery [59] reports good results in the treatment of gonorrheal epididymitis with sodium iodid. Ten cubic centimeters of a 10 per cent. solution is given intravenously every forty-eight hours until pain, tenderness and elevation of temperature have disappeared. The solution is given at room temperature and slowly. In no case has it been necessary to administer more than four injections. In all cases there was a decrease in intensity of pain and tenderness within twenty-four hours after the first injection.

[ED. NOTE.—Intravenous injections of various salt solutions have been used in the treatment of epididymitis with varying results during the last ten years. Sodium iodid can apparently be given intravenously without risk. As much as 400 c.c. of a 10 per cent. solution has been given at a single injection in the treatment of syphilis. It is necessary to proceed slowly and cautiously at first, using small amounts to make

59. Chenery, A. J.: Intravenous Treatment of Gonorrheal Epididymitis, U. S. Nav. Med. Bull. **21**:547-548 (Oct.) 1924.

certain that a reaction will not occur. Occasionally an idiosyncrasy will be seen, and it is not a desirable form of treatment in the presence of disease of the kidneys.]

EXPERIMENTAL VASOTOMY

Rolnick [60] reviews the results on forty-seven dogs of ninety-one vasotomies with the injection of various antiseptics. He attempted to determine the degree of permanent injury and the frequency of permanent occlusion after the injection of mercurochrome, mercurophen, meroxyl, collargol and chlorazene. These drugs were used in concentrations greater than the strength used in ordinary practice. He concludes that mercurochrome is not a safe antiseptic for vasotomy because it is an intense irritant to the vas and produces permanent occlusion in most cases. Meroxyl is more corrosive than mercurochrome. Mercurophen, although less irritating, will, if employed in sufficient therapeutic strength, cause occlusion in an appreciable number of cases. Collargol occludes often enough to suggest that it should be used with caution. Chlorazene in solutions of 1 : 1,000 to 1 : 4,000 can be employed without fear of permanent occlusion as a sequel.

PRERENAL ANURIA

Randall [61] discusses cases of anuria in which the fault lies with extra-urinary functions. This failure is in either the blood, vascular or nervous system. A blood pressure of 60 mm. of mercury is required in the afferent renal vessels to maintain urinary secretion. The normal glomerular pressure is about 90 mm. of mercury, or from 30 to 40 mm. below the normal blood pressure. Hypertension habituates the renal activity to a higher secretory pressure standard, and it is assumed that the threshold for anuria is correspondingly elevated. Anuria following changes in blood pressure is seen after sudden decompression of the overdistended bladder. Another pressure change causing anuria is that following closure of the suprapubic sinus after prostatectomy; with the reestablishment of intravesicular pressure the blood pressure may suddenly increase beyond the ability of a diseased heart to maintain adequate circulation. The part played in the secretory changes by the nervous system is difficult to separate from the other factors and still more difficult to demonstrate. Seres, in a recent article, shows that through the sympathetic nervous system, there is a close correlation

60. Rolnick, H. C.: Experimental Studies on the Vas Deferens, J. Urol. **12**:445-478 (Nov.) 1924.

61. Randall, Alexander: Prerenal Anuria, J. Urol. **13**:257-264 (March) 1925.

between distention of the bladder and renal function. That these organs do not function independently but in close coordination is likewise subjected to proof, and the polyuria which is produced by abrupt vesical distention and subsequent rapid evacuation fails to occur when this sympathetic nervous connection is broken. Through this study Seres outlines a method of overcoming anurias of nervous origin (hysterical anuria, reflex anuria or anuria due to excessive stimulation of inhibitory fibers) by means of repeated vesical distention and evacuation, or by gentle faradic stimulation of the wall of the bladder.

As regards the occurrence of true reflex anuria, by which is meant complete cessation of function in a healthy kidney following some catastrophe to its mate, Randall believes that we yet await the demonstration of a proved case. In treating this group of prerenal anurias, prevention is our object: careful support of the cardiovascular system; a large fluid intake; the avoidance, or removal, of any forms of splanchnic stimulation, and care in the administration of renal depressant drugs, especially pituitary extract and opiates. The anuric state of prerenal origin, when once established, should be handled by observing all these factors, and in addition it may be actively combated by three methods of attack: first, by vesical distention and rapid evacuation, as a possible stimulant to diuresis; second, by bilateral ureteral catheterization, which in all probability breaks an inhibitory arc which acts as the cause of the anuria, and third, by the established operation or renal decapsulation.

POSTRENAL ANURIA

Caulk [62] says that postrenal anuria, anuria due to disturbances of the excretory apparatus of the kidneys with discontinuance of the discharge of the urine, is usually the result of blocking of one or both of the ureters. The most frequent cause of such blocking is ureteral calculus. Caulk [62] also mentions accidental ligation of the ureter, suture of the vesical neck, packing and cauterization of the bladder, infiltration of the wall of the bladder, ureteral stricture, and occasionally ureteral catheterization and pyelography. This type of anuria is more amenable to treatment than the prerenal or renal anurias, provided one is familiar with the condition, appreciates the seriousness and institutes early treatment. The anuria may be entirely due to suppression, which according to Kümmel is a true postrenal anuria, but more frequently is associated with retention, a false anuria.

While the earlier writers on this subject believe that the immediate result of ureteral block was suppression, all the recent experimental and clinical evidence demonstrates conclusively that the majority of

62. Caulk, J. R.: Postrenal Anuria, J. Urol. **13**:265-281 (March) 1925.

such blocks are associated with retention in the renal pelvis, the kidney secreting within its pelvis, or ureter, until the intrarenal pressure is sufficiently high to prevent the process of urinary filtration and secretion. Retention predicts a much more favorable outlook, since its relief is usually quite promptly recompensed by resumption of secretion, and furthermore it indicates renal secretory activity. Uncomplicated postrenal anuria is in itself a very serious condition, chiefly because of its deception, since the patient, in spite of complete cessation of urinary elimination, may show no outward clinical evidence of danger. Most authors are unanimous in the belief that the majority of such anurias are due to mechanical obstructions or diseased kidneys, rather than to reflex inhibition of a normal kidney, although some cases of definite renorenal reflex seem to exist.

The evidence supporting the former idea is that no case of anuria following unilateral calculus has been reported in which a normal or only slightly diseased unobstructed kidney has been found at postmortem examination. Caulk is convinced, after a long series of experiments on animals, and from clinical observations, that reflex anuria must be extraordinarily rare, and if it ever does occur must find its explanation in circulatory changes. The treatment has been classified as expectant and surgical. At the present day such a classification does not seem tenable. Caulk feels that the two methods should be cystoscopic and operative. While a certain percentage of patients pass the calculus, the mortality is so high that watchful waiting is unjustifiable.

Success in the treatment of anuria depends on familiarity with the condition causing it, realization of its seriousness in spite of the comparatively good clinical condition of the patient, and prompt therapeutic measures. Expectant treatment should have a meager place in cases of anuria from calculus; with proper cystoscopic manipulations, stones may be removed, and anuria completely relieved in a fair number of cases. In other instances, by such methods, anuria may be temporarily relieved so that operation may be undertaken with less risk. In case of inability successfully and promptly to relieve the obstruction by cystoscopic technic, the surgeon of judgment, not deceived by the patient's apparently safe condition, will promptly remove the offending stone or stones by operation. The nature of the operation depends on the location and character of the calculus, just as it does in any other case of calculus of the kidneys and ureters. Under such a regimen one should expect a very low death rate in postrenal anuria, aside from the mortality incident to associated incorrectable maladies.

THE CASTS OF RENAL FAILURE

Addis [63] has shown that broad casts in the urinary sediment are an indication of partial or complete renal failure. When all the casts are very broad, the concentration of blood urea is more than 100 mg. for each 100 c.c. All patients with this condition died. The structure of these casts indicates that they are of cellular origin. They are formed in the larger collecting tubules or in the ducts of Bellini and occur in many diverse forms of renal injury. There are three varieties of broad casts, all different forms of the degeneration of a single type. The first or mother type is a cellular cast in which the nuclei of the cells can sometimes be made out. The second type is uncommon and is broad and waxy. The third type is the most common and is granular. At times this may be the only form that can be found.

UREA CONCENTRATION

Mills and Rabinowitch,[64] in a comparative study of the various tests of renal efficiency, find that in renal lesions associated with azotemia or any other evidence of impairment in the excretion of nitrogenous substances, the urea concentration factor is the most sensitive index. The test is carried out in the following manner: The patient is allowed no food or fluid of any kind after 6 p. m. the evening before the test. At 6 a. m. the day of the test the patient voids. This specimen is discarded. The patient is then given 15 grains (0.97 gm.) of urea dissolved in 150 c.c. of water. The blood is collected two hours after, and the urine at one and two hours after. The factor is obtained as follows: $\frac{\text{Milligrams of urea for each 100 c.c. of blood}}{\text{Milligrams of urea for each 100 c.c. of urine (second hour).}}$

The average normal value is 40. More recently, however, they have been attempting to find a still more accurate quantitative measure of the renal efficiency and have recommended obtaining a factor as follows: $\frac{\text{Urine urea concentration (2)}}{\text{Blood urea concentration}\frac{\text{before} + \text{blood urea}}{2}\text{concentration after}}$. In this way the mean blood urea concentration is used in the calculation. The normal value in this estimation is 50.

AIR EMBOLISM DURING URETHROSCOPY

Roper [65] reports the case of a man, aged 60 years, who complained of difficulty in micturition and gave a history of having passed pieces

63. Addis, Thomas: Renal Failure Cases, J. A. M. A. **84**:1013-1015 (April 4) 1925.

64. Mills, E. S., and Rabinowitch, I. M.: Observations on the Urea Concentration Factor in the Estimation of Renal Efficiency, Canad. M. A. J. **14**:915-916 (Oct.) 1924.

65. Roper, R. S.: A Case of Air Embolism Occurring During Urethroscopy, Lancet **1**:126 (Jan. 17) 1925.

of solid substance, which were probably blood clot. Physical examination revealed nothing abnormal. The urinary stream was small. A No. 10 (English) coudé catheter was passed with slight bleeding following. A urethroscope was passed and the urethra dried. A good view of the urethra was obtained under air inflation. The walls of the urethra in front of the bulb appeared covered with granulations which probably accounted for the ease with which bleeding occurred. No actual stricture was seen. When the urethroscope was removed, slight emphysema of the penis was seen. At the same time it was noticed that the patient was dazed, restless and constantly moving his head from side to side. He gradually lost consciousness and became cyanosed. The breathing became stertorous, then slow, and finally stopped; the pulse became feeble and was lost at the wrist. With artificial respiration, stimulants and oxygen sprayed over the face, he recovered.